A Novel Condensation during the Low-Pressure Hydrogenation of 5-Hydroxyisoquinoline

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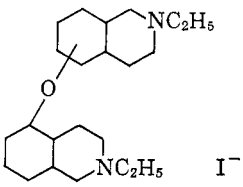
During the synthesis of some compounds designed to affect the cardiovascular system, it became necessary to examine hydrogenation procedures for 5-hydroxyisoquinoline. Two series of compounds were envisaged: first, 1,2,3,4-tetrahydroisoquinoline analogs and, second, the completely reduced decahydroisoquinoline derivatives. Hydrogenation of the isoquinoline nucleus to the tetrahydro stage from 5-hydroxy-2-ethylisoquinolinium bromide (VI) proceeded smoothly at low pressure using Adams platinum oxide as catalyst. It was conclusively shown that the hydrogenation of the salt (VI) proceeded more rapidly at 50 p.s.i. over platinum oxide (100% of total uptake in 0.5 hr.) than reduction of the free base, 5-hydroxyisoquinoline (22% of total uptake in 0.5 hr.), under identical conditions. In each case, the corresponding tetrahydro material was obtained from the reaction mixture in quantitative yield. This variation in the rate of hydrogenation is in agreement with the work of Lasslo and co-workers[1] who similarly found that various substituted pyridinium salts were hydrogenated more rapidly than the corresponding free bases, although emphasis was not placed on this feature in the accounts of their work.

For the complete saturation of the substituted isoquinolines discussed in this paper, the method outlined by Witkop[2] for the decahydrogenation of isoquinoline, *per se*, was chosen. It appeared to be the only direct method available, though several other indirect reductions to the decahydro stage have been reported.[3-11] Accordingly, 5-hydroxy-2-ethylisoquinolinium bromide (VI) was hydrogenated in glacial acetic acid containing a small amount of sulfuric acid using Adams platinum oxide catalyst. The reaction mixture yielded a bis(2-ethyldecahydroisoquinoline) ether (I); no other products were isolated by the above-described procedure.

Compound I was identified by its infrared absorption; the ether peak was clearly identified at 1110 cm.$^{-1}$ and there was no indication of the presence of a free hydroxyl function. The ultraviolet spectrum of the new ether did not show any absorptions, indicating complete saturation at the decahydro level. The postulated formula was further confirmed by preparing the corresponding quaternary diethiodide derivative (II); again spectrophotometric data was consistent with the proposed moiety.

Considering the prevailing reaction conditions, the spectroscopic and all other confirmatory evidence, it becomes apparent that we are dealing with an ether of 5-hydroxy-2-ethyldecahydroisoquinoline; the electrons of the other bond of the oxygen atom are shared with one of the carbon atoms of the alicyclic ring component of the second isoquinoline moiety. While it is probable that C-5 of the second isoquinoline nucleus is involved in the ether linkage, there is no direct evidence on this point.



I

$I^- (C_2H_5)_2\overset{+}{N}C_9H_{15}OC_9H_{15}\overset{+}{N}(C_2H_5)_2I^-$

II

No evidence has been found in the literature of this type of reductive condensation having been observed before. The formation of ethers under catalytically reductive conditions has been reported for some aliphatic and alicyclic ketones,[12] and reports have been noted of the formation of ethers by the reduction of acetals in acidic media.[13-15] One could not consider, however, the reduction of a heterocyclic phenol, wherein two independent molecules combine to yield an ether, comparable.

Further evidence that I is formed by reductive condensation was obtained by subjecting 5-hydroxy-2-ethyldecahydroisoquinoline (V) to the same acidic reaction conditions, including the presence of bromide ions (the hydrobromide salt of V was used), as those described for the preparation of I, but without the platinum oxide catalyst or hydrogen, for 48 hr. Careful isolation procedure yielded only the original starting material V.

Two factors may have contributed to the formation of I during the hydrogenation: (a) the presence of the alkyl substituent on the nitrogen atom, and (b) the nature of the anionic group. Attempts to evaluate the relative importance of these factors prompted us to investigate this matter further. First, the hydrogenation of the free base, 5-hydroxyisoquinoline, under *identical* conditions with those outlined for the preparation of I (see Experimental Section) resulted in 5-hydroxydecahydroisoquinoline (IV), and second, the *identical* hydrogenation of 5-hydroxy-2-ethylisoquinolinium hydroxide (see Experimental Section) yielded 5-hydroxy-2-ethyldecahydroisoquinoline (V). The results obtained from these additional experiments suggest that it is indeed the anionic group which influences the course of the reaction observed in the formation of ether I. The ionic moieties involved are shown in Figure 1. Only with the $N^+C_2H_5Br^-$ moiety was the anomalous ether formation observed.

The insolubility of corresponding iodides and chlorides (*i.e.*, 5-hydroxy-2-ethylisoquinolinium iodide and 5-hydroxyisoquinoline hydrochloride) in glacial

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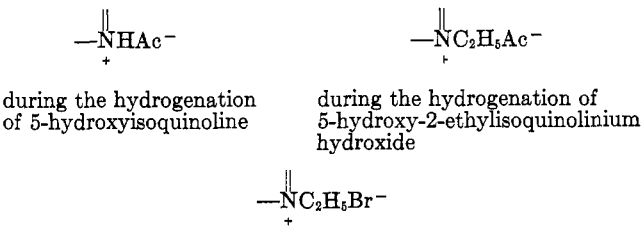

Figure 1

acetic acid did not permit an immediate study of the effect of other halide ions upon the reaction taking place during this hydrogenation. Further discussion of this subject matter is reserved for a future occasion.

Experimental Section[16]

5-Hydroxy-2-ethylisoquinolinium Bromide (VI).—5-Hydroxyisoquinoline (40 g., 0.28 mole) was dissolved in 100 ml. of absolute ethanol and refluxed for 8 hr. on a steam bath with 50% excess ethyl bromide (40 g., 0.37 mole). The ethanol and excess ethyl bromide was then evaporated off and the resulting brown solid was recrystallized from ethanol to yield 57.47 g. (82%) of light brown needles, m.p. 209.4–210.6°.

Anal. Calcd. for $C_{11}H_{12}BrNO$: C, 51.97; H, 4.73; Br, 31.50; N, 5.51. Found: C, 51.77; H, 4.68; Br, 31.50; N, 5.13.

5-(3,4,5-Trimethoxybenzoyloxy)isoquinoline (VII).—3,4,5-Trimethoxybenzoyl chloride (13 g., 0.057 mole), prepared according to the method of Lasslo and Jordan,[17] was dissolved in 200 ml. of sodium-dried benzene and 42 g. (0.29 mole) of 5-hydroxyisoquinoline, suspended in dry benzene, was added. The reaction mixture was then refluxed for 8 hr. The solid was filtered off; the benzene filtrate was evaporated to dryness; and the resulting solid was recrystallized from ethanol to yield 15.5 g. (87%) as pale yellow prisms, m.p. 198.5–199.0°.

Anal. Calcd. for $C_{19}H_{17}NO_5$: C, 67.24; H, 5.02; N, 4.13. Found: C, 67.39, H, 5.12; N, 3.90.

5-Hydroxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide (VIII).—5-Hydroxy-2-ethylisoquinolinium bromide (VI) (5 g., 0.0196 mole) was dissolved in 250 ml. of absolute ethanol and hydrogenated (Parr hydrogenation apparatus) over 300 mg. of Adams platinum oxide at 40 p.s.i. at room temperature. A white crystalline solid separated out when the hydrogenation was terminated (5 hr.). The hydrogenated suspension was heated on a steam bath until the precipitated solid had redissolved; the exhausted catalyst was then filtered off. The filtrate was concentrated, from which 4.5 g. (90%) of colorless plates crystallized on cooling, m.p. 223.8–224.6°. The ultraviolet spectrum of this compound had λ_{max} 272 and 277 mμ (log ε 3.24 and 3.23, respectively).

Anal. Calcd. for $C_{11}H_{16}BrNO$: C, 51.17; H, 6.20; Br, 31.01; N, 5.43. Found: C, 51.17; H, 6.06; Br, 31.28; N, 5.42.

5-(3,4,5-Trimethoxybenzoyloxy)-2-ethyl-1,2,3,4-tetrahydroisoquinoline Hybrobromide (IX).—5-Hydroxy-2-ethyl-1,2,3,4-tetrahydroisoquinoline hydrobromide (VIII) (4.3 g., 0.0166 mole) was dissolved in 100 ml. of water and sodium hydroxide solution was added until no further precipitation was evident. The resulting suspension was extracted with ether and dried, and the solvent was removed to yield 3.0 g. (100%) of white solid. This base was dissolved in 100 ml. of dry benzene and added to a solution of 4.0 g. (0.0173 mole) of 3,4,5-trimethoxybenzoyl chloride in 100 ml. of dry benzene. Two grams of dry sodium bicarbonate was added to this mixture, and the whole was refluxed for 8 hr. on a steam bath. The gelatinous precipitate which separated out was filtered (3.3 g.), and the filtrate was extracted with dilute hydrochloric acid. This acid extract, made alkaline with sodium hydroxide, was extracted with ether and dried. The ether was removed to yield 3.6 g. of a pale yellow oil. The hydrobromide salt of this base was recrystallized from ethanol–ether to yield 3.7 g. (32.3%) as short white needles, m.p. 213.2–213.4°.

Anal. Calcd. for $C_{21}H_{26}BrNO_5$: C, 55.75; H, 5.75; Br, 17.70; N, 3.10. Found: C, 55.59; H, 5.71; Br, 17.80; N, 3.18.

5-Hydroxydecahydroisoquinoline (IV).—5-Hydroxyisoquinoline (5 g.) was dissolved in 50 ml. of glacial acetic acid and 0.5 ml. of concentrated sulfuric acid was added. The resulting solution was hydrogenated over 5 g. of Adams platinum oxide at 50 p.s.i. for 36 hr. at room temperature. The exhausted catalyst was filtered from the hydrogenated solution, and the filtrate was diluted with approximately 50 ml. of water, made alkaline by the addition of sodium hydroxide pellets, and extracted with ether. The dried ethereal extract was evaporated carefully to yield a yellow oily residue (2.7 g.) which was treated with dry hydrogen chloride in ether to yield 2.9 g. (51%) of the base hydrochloride, recrystallized from ethanol–ether, m.p. 191.0–193.0°. The ultraviolet spectrum of this compound was taken in water and showed no absorption throughout the range 220–340 mμ.

Anal. Calcd. for $C_9H_{18}ClNO$: C, 56.25; H, 9.38; Cl, 18.75; N, 7.29. Found: C, 56.33; H, 9.43; Cl, 18.80; N, 7.22.

5-Hydroxy-2-ethyldecahydroisoquinoline (V).—5-Hydroxy-2-ethylisoquinolinium bromide (VI) (8 g., 0.031 mole) was treated with moist silver oxide (13 g., prepared from the action of sodium hydroxide on silver nitrate) in 100 ml. of a 50% aqueous methanol solution for 24 hr. The silver bromide formed was then filtered from the solution using Celite–charcoal mixture as a filter aid. The solvent was evaporated under reduced pressure at as low a temperature as possible to yield 5.7 g. (96%) of 5-hydroxy-2-ethylisoquinolinium hydroxide. The latter was hydrogenated as described in the preparation of IV. The base was converted to the hydrobromide, 5.62 g. (81%), which was recrystallized from ethanol–ether to yield fine white needles, m.p. 218.4–219.0°. The ultraviolet spectrum of this compound indicated no absorption in the range 220–310 mμ.

Anal. Calcd. for $C_{11}H_{22}BrNO$: C, 50.00; H, 8.33; Br, 30.31; N, 5.30. Found: C, 49.80; H, 8.31; Br, 30.38; N, 5.52.

5-(3,4,5-Trimethoxybenzoyloxy)-2-ethyldecahydroisoquinoline Hydrobromide (X).—5-Hydroxy-2-ethyldecahydroisoquinoline (V, 5 g., 0.027 mole) was dissolved in 20 ml. of sodium-dried toluene and added to a solution of 15 g. (0.065 mole) of 3,4,5-trimethoxybenzoyl chloride and refluxed for 48 hr. The resulting suspension was filtered, and the toluene filtrate was extracted with dilute hydrochloric acid. Neutralization of this acid extract was followed by extraction with ether. The ether extract was dried and evaporated to yield a brown viscous oil. This was purified by chromatography on a Florisil column and eluted with petroleum ether (b.p. 60–90°)–ether (10:1). Large prisms separated from the fractions on standing overnight. This material was crystallized from petroleum ether (b.p. 30–60°) to yield 4.52 g. (52%) of large prisms, m.p. 99.8–100.3°.

Anal. Calcd. for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 67.06; H, 8.32; N, 3.64.

One gram of the base was converted to the hydrobromide and recrystallized from ethanol–ether to yield 1.06 g. (88%) of short white needles, m.p. 197.8–198.6°.

Anal. Calcd. for $C_{21}H_{32}BrNO_5$: C, 55.02; H, 7.04; Br, 17.43; N, 3.06. Found: C, 55.12; H, 7.15; Br, 17.50, N, 3.11.

The Bis(2-ethyldecahydroisoquinoline) Ether I.—5-Hydroxy-2-ethylisoquinolinium bromide (VI, 5 g.) was dissolved in 50 ml. of glacial acetic acid with the aid of gentle heating on a steam bath. Concentrated sulfuric acid (0.5 ml.) was added and the mixture was hydrogenated over 5 g. of Adams platinum oxide at 50 p.s.i. for a period of 36 hr. at room temperature. The exhausted catalyst was filtered, and the acidic filtrate was diluted with water and made strongly alkaline by the addition of sodium hydroxide solution. The base was then extracted with ether and converted to the hydrobromide salt. Upon recrystallization from ethanol–ether, 2.14 g. (42%) of fine needles were obtained, melting at 196.6–197.1°. The ultraviolet spectrum of this compound showed no absorption through the range 220–310 mμ. The infrared spectrum (KBr) showed a medium absorption band at 1110 cm.$^{-1}$ in accordance with the absorption reported for an ether linkage.[18]

(16) Melting points were determined using a Swissco melting point apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 137B Infracord spectrophotometer. Ultraviolet data were recorded in aqueous solution using a Beckman ratio recording spectrophotometer, Model DK-2. Elemental analyses were carried out by Drs. G. Weiler and F. B. Strauss, Oxford, England.

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(18) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 115.

Anal. Calcd. for $C_{22}H_{42}BrN_2O$: C, 52.52; H, 8.29; Br, 31.31; N, 5.49. Found: C, 52.57; H, 8.48; Br, 31.20; N, 5.41.

In each of the three instances in which I was prepared, using identical reaction conditions, yields of 42%, or in excess thereof, were obtained.

Diethiodide of the Bis(2-ethyldecahydroisoquinoline) Ether (II).—The diethiodide derivative (II) of the above basic ether (I) was prepared by refluxing the free base, obtained from the neutralization of 1.0 g. of the bis(2-ethyldecahydroisoquinoline) ether dihydrobromide, dissolved in 25 ml. of dry benzene, for 4 hr. with excess ethyl iodide. The precipitated quaternary iodide was filtered and recrystallized from an alcohol–ether mixture to yield 0.93 g. (72%) of fine white needles, m.p. 245.0–245.4°. The infrared spectrum (KBr) showed a medium intensity absorption band at 1110 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{50}I_2N_2O$: C, 47.28; H, 7.63; I, 38.43; N, 4.24. Found: C, 47.28; H, 7.40; I, 38.20; N 4.27.

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6-Phenyltetrahydroquinoline

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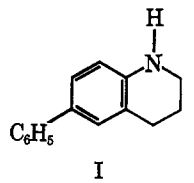
In 1885, LaCoste and Sorger[2] claimed to have prepared 6-phenyltetrahydroquinoline (I) by the reduction of 6-phenylquinoline with zinc and hydrochloric acid. They reported that the compound was unstable and that it was soluble in hot water but insoluble in chloroform and benzene. The only other reference to this compound appears to be in 1957 when Avramoff and Sprinzak[3] suggested that the instability claimed above might explain their failure to isolate the compound, as its picrate, on reduction of 6-phenylquinoline under conditions that gave 8-phenyltetrahydroquinoline from 8-phenylquinoline.



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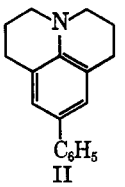

II

We have now prepared an authentic sample of the compound by the acid-catalyzed thermal decomposition[4,5] of N,N′-(*p*-biphenyl)-1,3-diaminopropane. It is a colorless crystalline solid, m.p. 79.5°, insoluble in hot water and freely soluble in benzene and chloroform. The infrared spectrum and elemental analyses are in accord with the structure. The compound seems as stable as similar tetrahydroquinolines, showing only a slight tendency to darken on exposure to air and light. It gives a picrate, m.p. 204°, and a benzoyl derivative, m.p. 142°, in contrast to LaCoste and Sorger's values of 165 and 137°, respectively. There seems little doubt that these workers had, at best, a very impure sample of the original compound.

The previously unreported 9-phenyljulolidine (II) was also obtained in the decomposition as expected.[4]

Experimental Section[6]

N,N′-Bis(*p*-biphenyl)-1,3-diaminopropane.—A solution of *p*-aminobiphenyl[7] (47.5 g.) and 1,3-dibromopropane (14.0 g.) in 70 ml. of benzene was refluxed for a total of 20 hr. The precipitated amine hydrobromides were twice removed during this time by adding 400 ml. of benzene and then washing with 10% aqueous sodium hydroxide solution before reducing the volume by distillation. The mixture was finally washed with aqueous alkali and with water and dried (K_2CO_3), and the excess *p*-aminobiphenyl (23.2 g.) was removed by distillation, b.p. 152–154° (1 mm.). The required compound was obtained as a yellow solid (10.2 g., 39%), b.p. 300–310° (0.5 mm.). It was washed with a little ether and then recrystallized from ethanol to give 7.5 g. of material, m.p. 111°.

Anal. Calcd. for $C_{27}H_{26}N_2$: C, 85.68; H, 6.92; N, 7.40. Found: C, 85.62; H, 7.06; N, 7.41.

6-Phenyltetrahydroquinoline. A.—The diaminopropane above (6.0 g.) was decomposed at 260–270° in the presence of 0.2 ml. of 48% hydrobromic acid by the method previously described.[4] An ethereal solution of the resultant distillate (5.0 g.) was washed with aqueous alkali and with water and the primary aromatic amines then removed by treatment[8] with 50% aqueous zinc chloride solution (2.52 g. of *p*-aminobiphenyl was recovered from the complex obtained). Distillation of the ethereal solution gave 1.0 g. (31%) of 6-phenyltetrahydroquinoline (b.p. 210–220° at 20 mm.).

B.—In a second preparation the intermediate diaminopropane was not isolated. *p*-Aminobiphenyl (60 g.), 1,3-dibromopropane (18 g.), and anhydrous potassium carbonate (18 g.) were heated together at 160° for 5 min. The mixture was then cooled and extracted by shaking with ether and water. The excess *p*-aminobiphenyl (32.5 g. recovered) was removed from the ether layer by shaking with aqueous zinc chloride solution. The crude diamine obtained after evaporation of the ether was decomposed as above and the *p*-aminobiphenyl formed was removed. Distillation then afforded the crude 6-phenyltetrahydroquinoline (4.1 g.), b.p. 150–189° (1 mm.). [The next fraction (3.0 g.), b.p. 190–192° at 1 mm., was 9-phenyljulolidine.] Redistillation gave the tetrahydroquinoline (2.2 g.) as an oil, b.p. 154–164° (1 mm.), which gradually solidified.

The 6-phenyltetrahydroquinoline was recrystallized from petroleum ether (b.p. 60–80°) to give colorless crystals, m.p. 79.5°. The infrared spectrum (melt) showed peaks at 3415 (N–H), 892 (isolated C_{Ar}–H), 825 (two adjacent C_{Ar}–H bonds), 761 and 698 cm.$^{-1}$ (monosubstituted benzene).

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.90; H, 6.98; N, 6.55.

The compound gave a benzoyl derivative, m.p. 142° from aqueous ethanol.

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.21; H, 6.02; N, 4.57.

It also gave a picrate, m.p. 203–204°.

Anal. Calcd. for $C_{21}H_{18}N_4O_7$: N, 12.78. Found: N, 12.85.

The 9-phenyljulolidine was recrystallized from petroleum ether to give colorless crystals, m.p. 69° (sharply depressed by addition of 6-phenyltetrahydroquinoline). The infrared spectrum had no peaks in the ranges 3600–3400 and 850–800 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.51; H, 7.68; N, 5.41.

It gave a methiodide, m.p. 210°.

(1) School of Chemical Sciences, University of East Anglia, Norwich, England.

(2) W. LaCoste and C. Sorger, *Ann.*, **230**, 1 (1885).

(3) M. Avramoff and Y. Sprinzak, *J. Org. Chem.*, **22**, 571 (1957).

(4) G. B. Russell, G. J. Sutherland, R. D. Topsom, and J. Vaughan, *ibid.*, **27**, 4375 (1962).

(5) I. K. Lewis, G. B. Russell, R. D. Topsom, and J. Vaughan, *ibid.*, **29**, 1183 (1964).

(6) Analyses were by the microanalytical laboratories at the University of Otago (Dr. A. D. Campbell) and Drs. G. Weiller and F. B. Strauss, Oxford. Infrared spectra were determined with a Perkin-Elmer 237 spectrometer.

(7) This compound is considered to be a dangerous carcinogen: private communication from Dr. R. A. M. Case, Chester Beatty Research Institute, London.

(8) See footnote 35 of ref. 5.