46 cm, at 25°, and voltages of −0.150 (sce) or −0.850 v (sce) and a drop time of 4.3 sec. The cell resistance, measured with a Wayne-Kerr Model B 221 universal impedance bridge, was always less than 50 ohms in McIlvaine buffer, consequently the $E°_{1/2}$ were not corrected for iR drop. The integrity of the reference calomel electrode was checked against a standard thallium sulfate solution. Using Triton X-100 as a maximum suppressor the average $E°_{1/2}$ was −0.459 ± 0.003 v in exact accordance with the literature value.[33]

Procedure.—The quinones were dissolved in McIlvaine buffer solutions in 50-ml volumetric flasks and transferred to the H cell after the pH had been checked on a Beckman Expandomatic pH meter. Triton X-100 (3 or 4 drops of 0.1% solution) was added, and the solution was deoxygenated for about 10 min with purified nitrogen[34] and then polarographed. The polarograms were analyzed graphically to determine the $E°_{1/2}$ and in certain cases the diffusion current (i_d) from the average of the recorder traces. The $E°_{1/2}$ values are accurate to ±0.003 v.

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ortho Claisen Rearrangement of Allyloxy-Substituted Isoquinolines[1]

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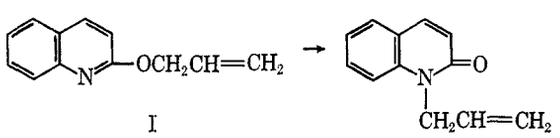
Thermal rearrangements of 3-allyloxyisoquinoline, 3-allyloxy-4-methylisoquinoline, and 1-allyloxyisoquinoline are reported. It is shown that the nature of the annular atoms adjacent to the allyloxy-substituted carbon in N-heteroaromatic allyl ethers does not play a significant role in the direction of the allyl group migration.

It has been observed that *ortho* Claisen rearrangements of 4-allyloxypyrimidines and 2-allyloxypyridines take place indiscriminately to the adjacent annular nitrogen and carbon.[2] Recently, Makisumi[3] reported that the thermal rearrangement of 2-allyloxyquinoline (I) gave N-allyl-2-quinoline (II) without a competing rearrangement to the 3 carbon.



I II

In this reaction the behavior of 2-allyloxyquinoline is similar to that of a number of other condensed ring allyl ethers, which rearrange to give only one product. For example, 2-allyloxynaphthalene rearranges to give only 1-allyl-2-naphthol[4] and 7-allyloxyquinoline rearranges to 8-allyl-7-quinolinol as the exclusive product.[5] In these systems, when the preferred rearrangement terminus is blocked by an allyl group, rearrangement to the alternative adjacent carbon does not occur and decomposition results. Therefore, if 2-allyloxyquinoline is considered as a model to compare with 2-allyloxynaphthalene, its annular nitrogen has replaced the favored α carbon in the naphthalene ring as a rearrangement terminus.

In previous reports, rearrangement to the adjacent annular nitrogen has always been observed.[2] However, no examples are available in which a nitrogen by analogy with 2-allyloxynaphthalenes is in the unfavored β' position as the rearrangement terminus. Allyloxyisoquinolines have this structural feature, and permit a comparison between the relative importance of nitrogen nucleophilicity and the naphthoid structural influence. For this reason it seemed pertinent to study the rearrangements of 1-allyloxyisoquinoline (III), in which the nitrogen occupies the favored position, 3-allyloxyisoquinoline (IV) in which the nitrogen is in an unfavorable ring position, and 3-allyloxy-4-methylisoquinoline (V) in which the potential carbon rearrangement terminus is blocked.

Results and Discussion

Allyloxyisoquinolines III, IV, and V were subjected to Claisen rearrangement conditions. Compound IV was prepared by treatment of 3-isoquinolinol[6] with allyl bromide and silver carbonate in dimethylformamide.[7] The isomeric alkylation product, N-allyl-3-isoquinolone, was not isolated using this method. Compound V was prepared from 3-amino-1-bromo-4-methylisoquinoline.[8] Hydrogenolysis employing palladium on charcoal followed by treatment with nitrous acid gave 3-hydroxy-4-methylisoquinoline which was converted into 3-allyloxy-4-methylisoquinoline by the method used for the preparation of IV. Compound III was prepared from 1-chloroisoquinoline[9] and sodium allyloxide.

Previous reports have shown that in 3-isoquinolinol and 1-methyl-6,7-dimethoxy-3-isoquinolinol, the amide structure predominates.[6,10] Spectral comparisons with 3-isoquinolinol and with 3-allyloxyisoquinoline indicate

(1) This investigation was supported by Public Health Service Research Grant No. GM-12112 from the National Institute of General Medical Sciences.

(2) (a) F. J. Dinan, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, **28**, 1015 (1963); (b) F. J. Dinan and H. Tieckelmann, *ibid.*, **29**, 892 (1964).

(3) Y. Makisumi, *Tetrahedron Letters*, **No. 39**, 2833 (1964).

(4) L. Claisen, *Ber.*, **45**, 3157 (1912).

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(7) These conditions were chosen because they have led to predominantly O alkylation of 2-pyridone with methyl iodide: G. A. Hopkins, Ph.D. Dissertation, State University of New York at Buffalo, Feb 1967.

(8) F. Johnson and W. A. Nasutavicus, *J. Org. Chem.*, **27**, 3953 (1962).

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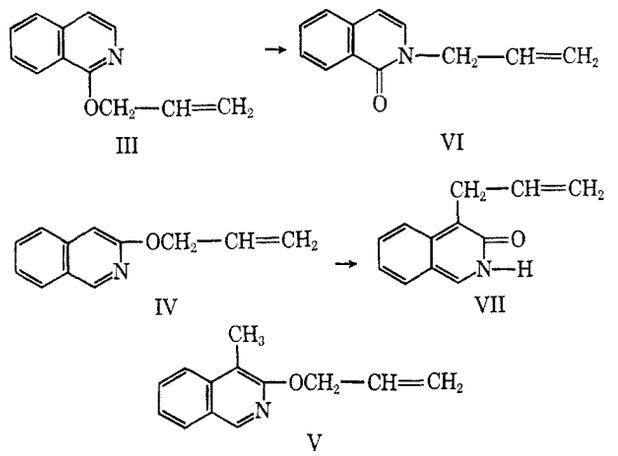
that 4-methyl-3-isoquinolinol (IX) and the rearrangement product VII also exist principally as amides.

Thermal rearrangement of neat III at 250° for 5 hr gave 94% of 2-allyl-1-isoquinoline (VI). Unrearranged III was recovered as the product balance.



Heating 3-allyloxyisoquinoline (IV) in 2-methylnaphthalene for 1 hr at 190° gave 56% of 4-allyl-3-hydroxyisoquinoline (VII) and 34% of unreacted ether. When V was heated under these conditions no rearrangement took place and the ether V was reclaimed quantitatively. A number of uncharacterized products were formed with higher temperatures and longer reaction times (heating for 5–6 hr. at 210–220°). The formation of significant amounts of N-allyl-4-methyl-3-isoquinoline was not observed. A small amount of material (<1%) which had spectroscopic properties consistent with those expected from an N-allyl-3-isoquinolone was isolated but was not conclusively shown to be this substance. Compound VII was soluble in dilute alkali. Comparison of nmr spectra of IV and VII showed that the allyl group in VII was on the C-4 position. The ultraviolet spectrum of VII closely resembled that of 3-hydroxyisoquinoline.[6]

The thermal rearrangement of 1-allyloxyisoquinoline (III) to N-allyl-1-isoquinolone (VI) demonstrates that the nitrogen of an allyloxy substituted isoquinoline can act as a normal rearrangement terminus.

The allyl groups of the ethers (I) and (IV) have both the adjacent carbon and nitrogen atoms available as potential rearrangement sites. Our thermal rearrangement data and that of Makisumi[3] clearly indicate that the high naphthoid specificity of the direction of migration is maintained and is uninfluenced by the nature of the adjacent annular atoms. This latter view is further substantiated by the observation that when the preferred position for the allyl group migration was blocked by a methyl group, as in the ether V, significant amounts of N-allyl compounds were not formed.

These observations indicate that the presence of an annular nitrogen adjacent to the allyloxy substituent or in another part of the condensed ring system[5] plays no significant role in directing the allyl group migration during the *ortho* Claisen rearrangement of the N-heteroaromatic allyl ethers.

The dominating influences which control the course of the allyl group migration during the thermal rearrangement of N-heteroaromatic allyl ethers appear to be the same as those which are operative in homoaromatic allyl ethers. The patterns of concerted reorganization of the bonding electrons and rehybridization of the bonding orbitals in the transition states are primary directional factors.

Experimental Section

Melting points are corrected and boiling points are uncorrected. Analyses were by Galbraith Laboratories, Knoxville, Tenn., Alfred Bernhardt, Mülheim, Germany, and Drs. G. Weiler and F. B. Strauss, Oxford, England.

Nmr spectra were obtained at 60 Mc on a Varian, Model A-60 spectrometer. Peak positions are reported in terms of parts per million from tetramethylsilane. Ultraviolet absorption spectra were determined on a Perkin-Elmer 202-UV-Vis spectrophotometer.

1-Allyloxyisoquinoline (III).—Metallic sodium (2.8 g, 0.12 g-atom) was dissolved in 50 ml of allyl alcohol (dried over Linde Molecular Sieve AW/500). The sodium allyloxide solution was filtered through glass wool into 40 ml of allyl alcohol containing 14.8 g (0.09 mole) of 1-chloroisoquinoline.[9] The reaction mixture was refluxed for about 5 hr. After removal of the allyl alcohol under reduced pressure, the residue was dissolved in water and extracted with ether. After the extracts were washed with water and dried, the solvent ether was removed. The 1-allyloxyisoquinoline was collected by distillation of the crude residue: yield 15.3 g (91%); bp 102–104° (1.5 mm); nmr spectrum (CCl_4) 5.12, 5.46, 6.25 (characteristic allyl multiplets, area 5), 7.0 (doublet, 1), 7.37 (multiplet, 3), 7.98 (doublet, 1), 8.20 (multiplet, 1); ultraviolet spectrum $\lambda_{max}^{95\%\ EtOH}$ 206, 216, 263, 273, 283, 310, 319, 323 mμ [ε (×10⁻³ mole⁻¹ cm⁻¹) 34.9, 32.5, 5.04, 6.74, 6.30, 3.52, 3.22, 3.44].

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 78.09; H, 6.01; N, 7.48.

3-Allyloxyisoquinoline (IV).—Silver carbonate (34 g, 0.12 mole) and 3-bromopropene (17.5 g, 0.14 mole) were added to a solution of 3-hydroxyisoquinoline[6] (18 g, 0.12 mole) in about 200 ml of degassed dimethylformamide. The reaction mixture was stoppered tightly and stirred overnight at room temperature. The solution was filtered and diluted with about 500 ml of water and extracted with ether. After the extracts were washed with water and dried, the solvent ether was removed. The pale yellow liquid analytical sample was distilled at 114–115° (0.15 mm), yielding 10.6 g (46%): nmr spectrum (CCl_4) 4.90, 5.36, 6.11 (characteristic allyl multiplets, area 5), 6.95 (singlet, 1), 7.47 (multiplet, 4), 8.66 (singlet, 1); ultraviolet spectrum $\lambda_{max}^{95\%\ EtOH}$ 206, 225, 265, 272, 275, 288, 337 mμ [ε (×10⁻³ mole⁻¹ cm⁻¹) 20.0, 66.6, 3.54, 3.35, 3.10, 1.51, 3.46].

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.75; H, 6.55; N, 7.34.

3-Amino-4-methylisoquinoline (VIII).—The compound was prepared from 3-amino-1-bromo-4-methylisoquinoline (2.5 g, 0.01 mole) by the method described by Johnson and Nasutavicus for the preparation of 3-aminoisoquinoline.[8] The analytical sample (pale yellow crystals) melted at 118–119°: yield 1 g (60%); nmr spectrum ($CDCl_3$) 2.29 (singlet, area 3), 4.54 (broad, 2), 7.42 (multiplet, 4), 8.76 (singlet, 1); ultraviolet spectrum $\lambda_{max}^{95\%\ EtOH}$ 208, 235, 275, 285, 295, 371 mμ [ε (×10⁻³ mole⁻¹ cm⁻¹) 20.5, 54.8, 5.12, 7.11, 5.81, 3.33].

Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.17; H, 6.36; N, 17.40.

4-Methyl-3-isoquinolinol (IX).—The compound was prepared from 0.84 g (5 mmoles) of VIII as described by Baumgarten, Murdock, and Dirks[6] for the preparation of 3-hydroxyisoquinoline. Extraction of the hydroxy compound with absolute ethanol[6] was avoided. Instead the crude product (0.96 g) IX was separated from inorganic salts by crystallization from chloroform. The yellow analytical sample melted at 191°: yield 0.70 g (82%); nmr spectrum (DMSO-d_6, 80°) 2.48 (singlet, area 3), 5.3 (broad), 7.67 (multiplet, 4), 8.82 (singlet, 1); ultraviolet spectrum $\lambda_{max}^{95\%\ EtOH}$ 202, 227, 236, 267, 282, 292, 306, 358, 416 mμ [ε (×10⁻³ mole⁻¹ cm⁻¹) 12.4, 40.8, 41.5, 3.13, 2.94, 3.17, 1.96, 1.80, 3.44].

Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.05; H, 5.68; N, 8.86.

3-Allyloxy-4-methylisoquinoline (V).—The compound was prepared from 6.4 g (0.04 mole) of 4-methyl-3-isoquinolinol (IX) by the method used for IV. The analytical sample, a light yel-

low liquid, was distilled at 124–125° (1.5 mm), yielding 4.0 g (50%): nmr spectrum (CCl_4) 2.38 (singlet, area 3), 5.08, 5.46, 6.21 (allyl multiplets, 5), 7.82 (multiplet, 4), 8.64 (singlet, 1); ultraviolet spectrum $\lambda_{max}^{95\%\ EtOH}$ 205 (shoulder), 226, 259, 270, 280, 293, 345 (broad) mμ [ε ($\times 10^{-3}$ mole^{-1} cm^{-1}) 17.6, 72.7, 3.27, 4.22, 4.74, 3.48, 4.89].

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.37; H, 6.57; N, 7.03. Found: C, 78.70; H, 6.75; N, 6.88.

Thermal Rearrangement of 1-Allyloxyisoquinoline (III).—Neat 1-allyloxyisoquinoline (III, 3.21 g) in a sealed tube was heated for 5 hr at 250°. The rearranged product was chromatographed on a silica gel column. Initial elution with chloroform recovered about 0.2 g (6%) of unrearranged material (III). Further elution with anhydrous ether afforded about 3.0 g (94%) of VI. The analytical sample distilled at 139–142° (1.5 mm): nmr spectrum (CCl_4) 4.60, 5.18, 5.95 (characteristic allyl multiplets, area 5), 6.38 (doublet, 1), 7.07 (doublet, 1), 7.46 (multiplet, 3), 8.46 (multiplet, 1); ultraviolet spectrum $\lambda_{max}^{95\%\ EtOH}$ 207, 225, 239, 249, 279, 288, 315, 325, 348 mμ [ε ($\times 10^{-3}$ mole^{-1} cm^{-1}) 44.3, 23.3, 10.4, 7.76, 9.72, 9.72, 4.46, 5.21, 3.65].

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.99; H, 6.29; N, 7.59.

Thermal Rearrangement of 3-Allyloxyisoquinoline (IV).—A 0.5-ml aliquot (0.51 g) from a stock solution of 1.314 g of IV in 3.146 g of 2-methylnaphthalene was heated in a sealed tube at 190° for 1 hr. Vpc analysis of the rearranged mixture gave 56% of 4-allyl-3-hydroxyisoquinoline (VII) and 34% of unrearranged IV.

Vpc Analytical Method.—The rearranged product in 4.0 ml of chloroform was analyzed by F & M Model 720 gas chromatograph equipped with a 2 ft × 0.25 in. o.d. stainless steel column. The columns were packed with 10% silicone gum rubber (SE-30) silanized Chromosorb W[11] mesh 60–80. The temperature was programmed from 150 to 300° at 10°/min with a helium flow rate of 60 ml/min. Samples of 30–40 μl were generally injected. Product distribution was determined by standard procedure employing prepared mixtures of pure materials (starting ether and 2-methylnaphthalene and rearranged product) and solvent chloroform of known composition approximating that obtained upon thermal rearrangement under the experimental conditions. The error of the analytical method is estimated to be ±5%.

Isolation and Identification of 4-Allyl-3-hydroxyisoquinoline (VII).—The rearranged mixture was passed through a silica gel column (100–200 mesh). The unrearranged ether (IV) and solvent for the rearrangement (2-methylnaphthalene) were eluted with hexane. The yellow rearranged product (VII) was obtained by further eluting the column with a mixed solvent of anhydrous ether–hexane (8:2). The eluting solvent was removed by flash distillation. The analytical sample of the rearranged product (VII) was obtained by crystallization from acetone as yellow, fine crystals: mp 173°; nmr spectrum (DMSO-d_6, 80°), 3.73 (multiplet, area 2), 5.05 (multiplet, 2), 5.48 (very broad, 1), 6.05 (multiplet, 1), 7.57 (multiplet, 4), 8.81 (singlet, 1); ultraviolet spectrum $\lambda_{max}^{95\%\ EtOH}$ 228, 237, 268, 280, 291, 306, 357, 418 mμ [ε ($\times 10^{-3}$ mole^{-1} cm^{-1}) 41.5, 40.1, 3.40, 3.09, 3.21, 1.83, 1.95, 3.63].

Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.60; H, 5.94; N, 7.58.

Attempted Thermal Rearrangement of 3-Allyloxy-4-methylisoquinoline (V).—The ether V (1.05 g) in 2.48 g of 2-methylnaphthalene in a sealed Pyrex glass tube was heated for 5–6 hr at 210° in a thermostated oil bath. The mixture was washed with petroleum ether (bp 30–60°) in several portions. The petroleum ether washings were combined and evaporated under reduced pressure. Vpc analysis of the residue (2.58 g) revealed that it contained only the unrearranged ether V (0.1 g) and the solvent, 2-methylnaphthalene. The petroleum ether insoluble portion of the rearranged product (0.79 g) was taken in chloroform and washed several times with (1) 1 *N* hydrochloric acid, (2) 1 *N* ammonium hydroxide, and (3) water and dried over anhydrous sodium sulfate. The washed residue, about 0.5 g (mp 120–137°), was obtained after the chloroform was removed by flash distillation. Silica gel thin layer chromatographic analysis of this washed residue revealed it to be a mixture of several compounds all in small amounts. This and the residue obtained from the preparation of ether V contained identical spots at R_f 0.7 and had similar ultraviolet absorption spectra. Estimates based on the ultraviolet absorbance at 207 mμ of this indicated that less than 1% of N-allyl-4-methyl-3-isoquinolone might be present.

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