The Ultraviolet Absorption Spectra of Some Monofluoroisoquinolines

BY SAMUEL B. KNIGHT, WILLIAM K. MILLER AND ARTHUR ROE

In previous papers the ultraviolet absorption spectra of the monofluoroquinolines were reported,[1] and the data were utilized to determine basic dissociation constants of the compounds[2] and to study the hydrolysis of 2-fluoroquinoline in acid solution.[3] The applicability of these results suggested that a similar study of the monofluoroisoquinolines would be desirable. This paper will be confined to the three isomers in which the fluorine atom is in the pyridinoid ring. The absorption spectra of these compounds as well as that of isoquinoline were measured in the same solvents in which those of the fluoroquinolines were measured,[1] and the maxima obtained in the various solvents are reported in Table I.

TABLE I

SPECTRAL DATA OF SOME FLUOROISOQUINOLINES[a]

Compound	Maxima: λ in mμ, ε × 10⁻³ In 95% ethanol	In 10% ethanol	In 0.01 *M* HCl[b]
Isoquinoline	268 (3.56), 319 (2.79)	268 (3.29), 319 (2.67)	275 (1.94), 329 (3.86)
1-Fluoroisoquinoline	265 (4.14), 317 (2.96)	265 (3.92), 318 (3.00)	272 (6.78), 324 (4.63)
1-Hydroxyisoquinoline			272 (6.77), 324 (4.61)
3-Fluoroisoquinoline	270 (2.83), 326 (3.20)	270 (2.61), 325 (3.12)	[c]
4-Fluoroisoquinoline	270 (4.10), 320 (3.09)	270 (3.90), 321 (3.09)	274 (2.39), 333 (4.80)

[a] The spectra in 10% ethanol which is 0.01 *M* with sodium hydroxide is almost identical with that in 10% ethanol. [b] The HCl solution contains 10% ethanol by weight. [c] Identical with that in 10% ethanol.

Spiers and Wibaut[4] found that a halogen atom, when substituted in the pyridine nucleus, tended to produce both a bathochromic shift and an increase in intensity of the maximum absorption band, the displacement appearing greater when the halogen was closer to the nitrogen atom. No such systematic shifts of absorption were evident when a halogen was introduced into the quinoline nucleus.[1] Similarly, no definite pattern of absorption was found with the three fluoroisoquinolines as is evidenced in Fig. 1.

The ultraviolet spectrum of isoquinoline in 95% ethanol exhibits two distinct maxima (Fig. 1) beyond 230, at 268 and 319 mμ. The extinction coefficients at these wave lengths are 3.56 and 2.79 × 10^3, respectively. Of the three fluoroisoquinolines whose spectra were measured, the 3- and 4-isomers exhibited bathochromic shifts of the first (268 mμ) maximum, while a hypsochromic shift was found in the spectrum of the 1-isomer. Increases in extinction at the first maximum were evident in the spectra of the 1- and 4-fluoroisoquinolines, but a marked decrease in intensity of absorption was found in the spectrum of the 3-isomer. Shifts of the second maximum were similar to those of the first, with the single exception that all of the isomers exhibited increases in extinction coefficient at the band of longer wave length. On the basis of these and previous results[1] it would not be feasible to predict the effect of the introduction of the fluorine atom into the four benzenoid ring positions of the isoquinoline nucleus. The latter study will have to await preparation of the remaining isomers.

The ultraviolet absorption spectra of isoquinoline, 3-fluoroisoquinoline, 4-fluoroisoquinoline and 1-fluoroisoquinoline in 95% ethanol, 10% ethanol, and 10% ethanol which is 0.01 *M* with HCl are shown in Figs. 2A, 2B, 2C and 3, respectively. The differences between the spectra in 95% ethanol and in 10% ethanol are slight but are quite similar for each compound and could be explained by possible solvate formation[1] or by the difference in polarity of the two solvents.

The differences between the spectra of the compounds in neutral and in 0.01 *M* HCl solutions are significant. The spectrum of isoquinoline in neutral or basic solution represents the absorption of the molecule, while that in 0.01 *M* HCl solution represents the absorption of the isoquinolonium ion, since the hydrochloride is formed in acid solution. A similar effect on the spectrum of 4-fluoroisoquinoline is observed in passing from neutral to acid solution. Hence, as would be ex-

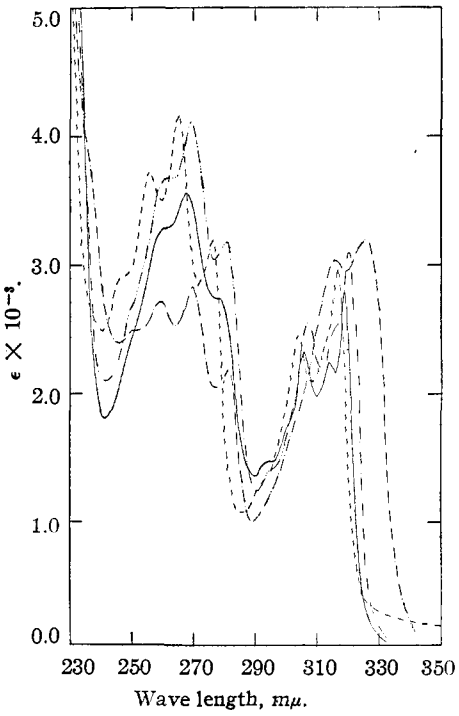

Fig. 1.—Ultraviolet absorption: ——, isoquinoline; – – –, 1-fluoroisoquinoline; —·—, 3-fluoroisoquinoline; —···—, 4-fluoroisoquinoline; in 95% ethanol.

(1) W. K. Miller, S. B. Knight and A. Roe, THIS JOURNAL, **72**, 1629 (1950).
(2) W. K. Miller, S. B. Knight and A. Roe, *ibid.*, **72**, 4763 (1950).
(3) W. K. Miller, S. B. Knight and A. Roe, *ibid.*, **72**, 4765 (1950).
(4) C. W. F. Spiers and J. P. Wibaut, *Rec. trav. chim.*, **56**, 573 (1937).

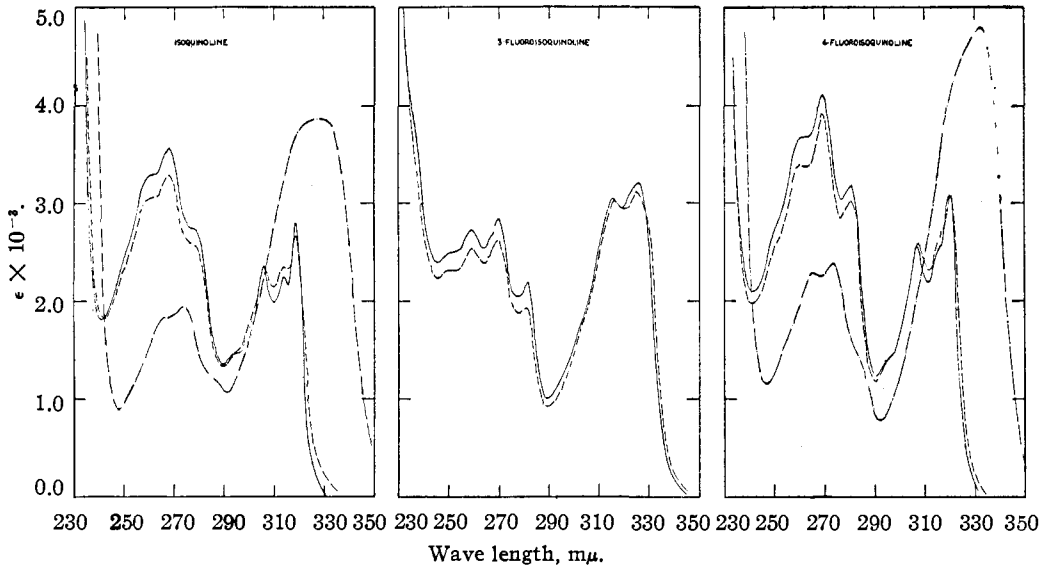

Fig. 2.—Ultraviolet absorption: ———, 95% ethanol; - - - - - -, 10% ethanol; —·—·—, 10% ethanol 0.01 *M* with HCl.

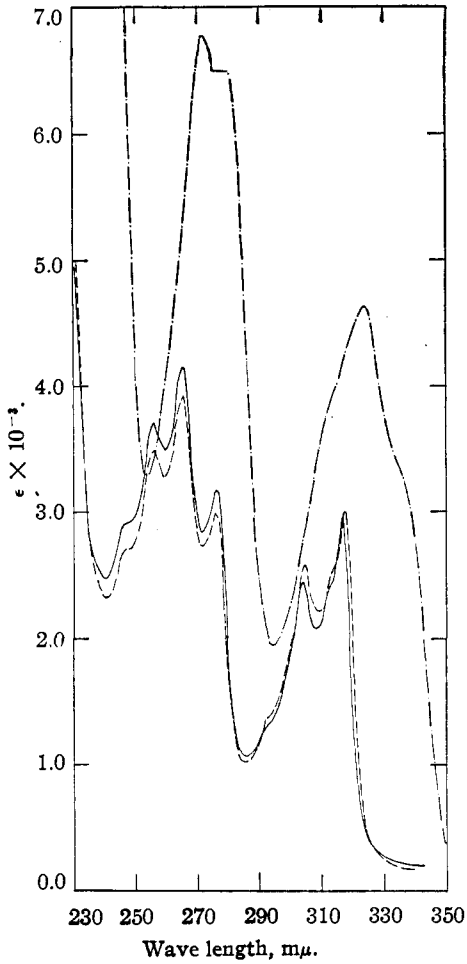

Fig. 3.—Ultraviolet absorption: 1-fluoroisoquinoline: ———, 95% ethanol; - - -, 10% ethanol; —·—, 10% ethanol which is 0.01 *M* with HCl.

pected, it is apparent that the latter compound is basic enough to form a hydrochloride.

Roe and Hawkins[5] reported that the 2-fluoro derivatives of both pyridine and quinoline were insoluble in dilute HCl, indicating that they were too weakly basic to form hydrochlorides. It would be reasonable to predict that the 1- and 3-fluoroisoquinolines would react similarly, since, in these isomers, the fluorine atom is attached to the carbon atom adjacent to the nitrogen as in 2-fluoroquinoline. No shift of the spectrum of 3-fluoroquinoline was evident in passing from neutral to 0.01 *M* HCl as solvent, indicating that no hydrochloride was formed. A marked shift of the absorption center of the 1-isomer occurred, but this was caused by hydrolysis of the compound in acid solution instead of hydrochloride formation.

In a previous paper[3] it was shown that 2-fluoroquinoline hydrolyzed in acid solution to 2-hydroxyquinoline. This suggested that both the 1- and 3-fluoroisoquinolines might react similarly since the fluorine atoms in these two compounds are situated the same as that in 2-fluoroquinoline with respect to the nitrogen atom. The spectrum of 1-fluoroisoquinoline in 0.01 *M* HCl solution was found to be identical with that of 1-hydroxyisoquinoline in the same solvent as measured by Ewing and Steck[6] and repeated by the authors. However, there was no shift of absorption of 3-fluoroisoquinoline in passing from neutral to acid solution as the solvent, revealing that the latter compound is not hydrolyzed in acid solution.

No attempt is made here to give an interpretive discussion of the data. Such a discussion should await the gathering of more data on many other heterocyclic halogen compounds, when perhaps worthwhile correlations can be made.

Experimental

Absorption Spectra.—The spectra were measured and plotted using the same technique as previously described;[1] the solvents were also the same.

Isoquinoline.—A synthetic Eastman Kodak Co. product

(5) A. Roe and G. F. Hawkins, THIS JOURNAL, **69**, 2443 (1947); **71**, 1785 (1949).

(6) G. W. Ewing and E. A. Steck, *ibid.*, **68**, 2181 (1946).

was dried over sodium hydroxide and distilled under reduced pressure.

All of the fluoroisoquinolines and 1-hydroxyisoquinoline were prepared in this Laboratory[7] and were redistilled until the absorption spectra of successive distillates were identical.

Acknowledgment.—This work is part of a study of the preparation and properties of heterocyclic fluorine compounds being carried out in this laboratory, and was supported in part by the Office of Naval Research, Contract No. N8onr-69900.

(7) A. Roe and C. E. Teague, THIS JOURNAL, **73**, 687 (1951).

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Sterols of Algae. III.[1] The Occurrence of Ergosterol in *Chlorella pyranoidosa*[2]

BY MARYLIN KLOSTY AND WERNER BERGMANN

It was reported in the first communication of this series,[3] that chondrillasterol is the principal sterol of the green alga, *Scenedesmus obliquus*. This sterol is of special interest because it is a $\Delta^{7,22}$-diene-3-ol and therefore potentially suitable for conversion into cortisone by methods now being investigated in several laboratories. The amount of chondrillasterol obtainable from *Scenedesmus*, however, appears too small to be of practical significance at this time. The studies on algae sterols have now been extended to other primitive algae of the class of *Chlorophyceae*, and in particular to those, whose commercial cultivation is contemplated by several organizations.

Through the courtesy of the Lederle Laboratories Division[4] the authors obtained several pounds of freeze-dried cells of a pure culture of the green alga, *Chlorella pyranoidosa*. Upon acetone extraction, the algae yielded 12.5% of lipoid material, of which 10% was unsaponifiable. The sterol content of the unsaponifiable fraction was approximately 20%, corresponding to 0.15–0.2% of the dry alga. A more efficient extraction was achieved when the cells were first triturated with warm glacial acetic acid and then exhaustively extracted with acetone. Cells so treated yielded a lipoid and sterol fraction corresponding, respectively, to 20 and 0.4%. The sterols were isolated from the unsaponifiable fraction either by precipitation with digitonine, by direct crystallization or better by way of their benzoates. The high negative rotation and the ultraviolet absorption spectra of the crude fractions indicated the presence of $\Delta^{5,7}$-sterols in excess of 75% of the mixture. Repeated recrystallizations of the benzoates eventually afforded ergosteryl benzoate, m.p. 169°; $[\alpha]^{25}D$ −72°. It was converted to ergosterol, m. p. 164°; $[\alpha]^{25}D$ −128°, and ergosteryl acetate, m.p. 176°; $[\alpha]^{25}D$ −88°.

Chlorella pyranoidosa appears to be the first organism other than fungi and lichens in which ergosterol has been shown to be the principal sterol.[5] As a minor component, 0.1–5%, ergosterol has been found in the sterol mixtures from cocksfoot,[6] cottonseed oil,[7] scopolia root oil[7] and wheat germ oil.[8] More substantial amounts of ergosterol have been found in the sterol mixtures from certain animals,[9] in particular invertebrates.[10]

Experimental

The following extraction procedure was found to be the most efficient. Fifty grams of freeze-dried cells of *Chlorella pyranoidosa*, which contained about 10% of moisture, was heated for one hour at 70° with 100 ml. of glacial acetic acid. The acid was then removed by freeze-drying, and the residue ground, and extracted in a Soxhlet apparatus with acetone for 24 hours. The extract was filtered to remove some amorphous, gray solid (1.5 g.), and the solvent was removed first by distillation and finally by freeze-drying. The extract thus obtained, 10 g., was saponified under nitrogen with 45 g. of a 20% solution of potassium hydroxide in 80% ethanol. After 24 hours 150 ml. of water was added, and the solution extracted seven times with 100-ml. portions of peroxide-free ether. The combined ether layers were washed with water and concentrated under nitrogen. After freeze-drying, the residue weighed 1.5 g. The sterol content of the residue, as determined by the digitonide method, was 13.4%, corresponding to 0.4% of the algae.

The unsaponifiable fraction obtained from several hundred grams of algae was dissolved in a minimum amount of boiling methanol. Upon cooling a waxy, crystalline material was obtained in a yield of 23%. It was dissolved in anhydrous pyridine and treated with an excess of benzoyl chloride for 24 hours at room temperature. The mixture was then poured into methanol, and the precipitate, m.p. 144–156°, recrystallized from ether–methanol; yield 11% of unsaponifiable fraction; m.p. 156–162°; $[\alpha]^{25}D$ −58. Several recrystallizations from dioxane–methanol and ethyl acetate afforded ergosteryl benzoate, m.p. 169°; $[\alpha]^{25}D$ −72° in chloroform. The ultraviolet absorption spectra indicated a purity in excess of 95%.

Anal. Calcd. for $C_{35}H_{44}O_2$: C, 84.00; H, 9.60. Found: C, 83.75; H, 9.93.

The benzoate was refluxed for one hour with a 3% solution of potassium hydroxide in ethanol in an atmosphere of nitrogen. The solution was then diluted with water, and the precipitated ergosterol was recrystallized several times from acetone and ethyl acetate, m.p. 162°; $[\alpha]^{25}D$ −128° (chloroform). Acetylation by reflux with acetic anhydride afforded ergosteryl acetate, m.p. 176°; $[\alpha]^{25}D$ −92° (chloroform). None of the products gave depressions of melting points when mixed with authentic material.

(1) Paper II, THIS JOURNAL, **73**, 2395 (1951).

(2) This investigation was supported by a research grant from the National Institute of Health, Public Health Service.

(3) W. Bergmann and R. J. Feeney, *J. Org. Chem.*, **15**, 812 (1950).

(4) American Cyanamid Co., Pearl River, New York.

(5) The statement made in Elsevier's "Encyclopaedia of Organic Chemistry," Vol. **14**, 69 (1940), that ergosterol is present in the brown alga, *Fucus crispus*, is in error. It is based on a brief note by Gérard (*Compt. rend.*, **126**, 909 (1898)) which states that the sterol of *Fucus* gives color reactions reminiscent of those shown by sterols from cryptogams. Since then it has been shown that fucosterol is the principal sterol of this alga.

(6) A. Pollard, *Biochem. J.*, **30**, 382 (1936).

(7) A. Windaus and F. Bock, *Z. physiol. Chem.*, **250**, 258 (1937).

(8) A. Windaus and F. Bock, *ibid.*, **256**, 47 (1938).

(9) A. Windaus and O. Stange, *ibid.*, **244**, 218 (1936)

(10) F. Bock and F. Wetter, *ibid.*, **256**, 33 (1938).

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[FROM THE CHEMICAL LABORATORY OF THE ACADEMY OF COMMERCE IN VIENNA]

Bromination of Resorcinol Monomethyl Ether and Debromination of Tribromoresorcinol Monomethyl Ether

BY MORITZ KOHN

The bromination of resorcinol monomethyl ether with two molecules of bromine yields a crys-