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Synthesis and Nucleophilic Displacement Reactions of Fluoropyrazine and 2-Fluoroquinoxaline

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An improved method for the preparation of fluoropyrazine (I) by halogen exchange and a synthesis of 2-fluoroquinoxaline (II) by a Balz-Schiemann reaction are presented. Compound I hydrolyzes slowly in 0.01*N* sodium hydroxide, rapidly in 1.07*N* sodium hydroxide at 26.00°. Compound II hydrolyzes 240 times faster than I in 0.01*N* sodium hydroxide at 26.00°. Hydrolysis of I in 6*N* hydrochloric acid at room temperature is slow. Compound I underwent nucleophilic reactions with formation of hydroxy, amino, methylamino, piperidino, benzylamino and anilinopyrazines. Pyrazinesulfonic acid was obtained from I and sodium sulfite and tetrazolo[1,5-*a*]pyrazine (IV), a novel ring system, from I and sodium azide.

Chloropyrazine and 2-chloroquinoxaline serve as useful intermediates by virtue of their relatively facile reaction with nucleophiles. Both are readily accessible from the corresponding hydroxy derivatives by treatment with phosphorus oxychloride (2,3). Similarly bromopyrazine has been obtained from pyrazinol and phosphorus oxybromide/phosphorus pentabromide (2). Iodopyrazine is best prepared by halogen exchange from chloropyrazine and sodium iodide (4). A preparation of 2-bromoquinoxaline is given in the patent literature (5), while 2-iodoquinoxaline has not yet been reported.

As reported earlier (6), fluoropyrazine (I) was prepared by a Balz-Schiemann reaction from aminopyrazine in 23% yield. Subsequent work led to the successful application of the halogen exchange method (7). Treatment of chloropyrazine with anhydrous potassium fluoride in refluxing dimethyl sulfoxide for 2 hours followed by double fractionation afforded fluoropyrazine in 57% yield. This approach, unlike the Balz-Schiemann method, is readily adaptable to preparative scale-up.

The Balz-Schiemann reaction also was found applicable to the synthesis of 2-fluoroquinoxaline (II) from 2-aminoquinoxaline in 30% yield. However, the markedly greater reactivity of II towards nucleophiles necessitated low-temperature extraction of the diluted reaction mixture without prior neutralization as in the case of I. Washing and drying operations were also done at 0-5° to minimize losses through hydrolysis. Fractionation afforded 2-fluoroquinoxaline, a colorless liquid, boiling at 96-96.5°/11 mm. Slight discoloration and decomposition with formation of colorless needles occurred on storage at room temperature for one month. Preparation of II by halogen exchange was not attempted.

The nuclear magnetic resonance (NMR) spectrum of II in carbon tetrachloride shows a sharp doublet at 8.56 ppm (J = 8 c.p.s.) due to the proton in the 3-position. The chemical shift for pyrazine in deuteriochloroform is 8.60 ppm, and 8.84 ppm for the corresponding protons of quinoxaline (8). The remainder of the spectrum, an envelope in the region 7.4-8.1 ppm, is characteristic of aromatic protons. Integration gave a ratio of 4.1 to 1. The coupling constant $J_{3,F}$ of II agrees well with the reported *ortho* $J_{H,F}$ in fluorobenzene ($J_{H,F}$ = 6-10 c.p.s.) (9), but is considerably larger than $J_{3,F}$ in 2-fluoropyridine (2.8 c.p.s.) (10). The NMR spectrum of I in carbon tetrachloride shows several closely-spaced overlapping peaks which have not yet been assigned.

A limited number of halogenated heterocyclic compounds were hydrolyzed under controlled conditions in order to obtain a measure of their relative reactivities towards nucleophiles. The process of hydrolysis was selected to permit direct measurement of the extent of reaction by ultraviolet methods,

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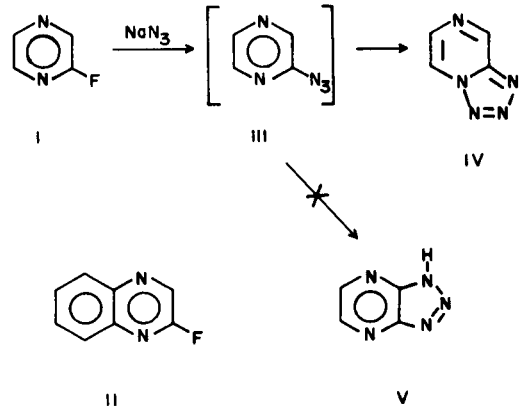


since the resultant hydroxy compounds generally possess spectra sufficiently different from those of the starting materials (11).

Hydrolysis of I in excess 1.07*N* sodium hydroxide at 26.00 ± 0.03° proceeded rapidly following pseudo-first order kinetics. Duplicate experiments gave a half-life ($t_{1/2}$) of 42.7 minutes (±4%). Under similar conditions (1.07*N* sodium hydroxide, room temperature) chloropyrazine had a half-life of *ca.* 19 days, while iodopyrazine and 2-fluoropyridine remained essentially unchanged. Hence, I is 640 times more reactive than chloropyrazine. In 0.01*N* sodium hydroxide at room temperature, I reacted slowly ($t_{1/2}$ = *ca.* 7 days). In contrast, II had a half-life of 42.5 minutes (±2%) in the same medium at 26.00 ± 0.03°. Hence, ring annelation leads to a 240 fold increase in reactivity. This observation is in agreement with the recent report of the high susceptibility of 2,3-difluoroquinoxaline towards hydrolysis resulting in formation of 2,3-dihydroxyquinoxaline in nearly quantitative yield under the conditions of a steam distillation (12).

Acid hydrolysis of I in 6*N* hydrochloric acid at room temperature was slow ($t_{1/2}$ *ca.* 4 days). This result was surprising in view of the generally greater susceptibility of halopurines and halopyridines to acid hydrolysis than to alkaline hydrolysis (13). 2-Fluorohypoxanthine was found to be readily hydrolyzed to xanthine in 0.1*N* hydrochloric acid at room temperature, but it was stable in 0.1*N* sodium hydroxide (14). Halopyridines, notably 2- or 6-substituted fluoro derivatives, were more easily hydrolyzed in acid than in basic media (15). A possible explanation may lie in the magnitude of the ionization constants (pK_a) of the substrates. The pK_a values of pyridine, 2-fluoropyridine and pyrazine are 5.2, -0.4 and 0.6, respectively (16). The pK_a for I is not known, but it is probably less than -0.4.

In 6*N* hydrochloric acid, 2-fluoropyridine is partially protonated, and nucleophilic attack by water would be facilitated. However, I probably exists chiefly as the neutral species in both acid and basic media and would be expected to react more readily with hydroxyl ion, the stronger of the two nucleophiles. The kinetic data are summarized in Table I.

The high ratio of the reactivity of fluoropyrazine to chloropyrazine (*ca.* 640 to 1) indicates bond-making predominates in the rate-determining step of the reaction with hydroxyl ion, *i.e.*, addition is the slow step followed by rapid elimination of fluoride ion (17). The energetics of solvation and of hydrogen bonding of the incipient fluoride ion are particularly favorable in aqueous media and may, in part, be responsible for the observed sharp decrease in the rate of ammonolysis of I in methanol and in benzene relative to water. Comparable activation of fluorine relative to chlorine has been observed for 4-halonitrobenzenes in the reaction with sodium ethoxide in ethanol (230:1) (18) and for 1-halo-2,4-dinitrobenzenes in the reaction with piperidine in ethanol (750:1) (19,20).

The facile displacement of fluorine from I by nucleophiles was utilized in the preparation of a number of substituted pyrazines. Several of these compounds had previously been prepared from chloropyrazine permitting comparisons of the relative reactivities of the two starting materials towards various nucleophiles. The results indicate significantly greater susceptibility of I not only towards alkaline hydrolysis but also towards ammonolysis, aminolysis and reaction with sodium sulfite. Aminolysis with methylamine, piperidine, and benzylamine in methanol proceeded readily at room temperature in 3 days with formation of the corresponding substituted aminopyrazines in 88%, 95% and 74% yields, respectively. Methylaminopyrazine had previously been obtained in 67% yield from chloropyrazine under forcing conditions (150°, 7 hours) (21). Compound I reacted with the weak nucleophilic aniline at 130-135° (3-9 hours) to give anilinopyrazine in 20-24% yield.

Reaction of I with excess sodium azide in refluxing 80% ethanol afforded a 36% yield of tetrazolo[1,5-*a*]-pyrazine (IV), a novel ring system, probably resulting from cyclization of the intermediate azidopyrazine (III). Formation of tetrazoles in preference to the azido derivatives has been observed for other nitrogen heterocycles, *e.g.* pyridines, quinolines, purines (22).

Assignment of structure IV is based on the following evidence. Infrared spectroscopy showed absence of a band near 2100 cm^{-1} characteristic of the azido function (23), hence III was eliminated. Triazole V was ruled out on the basis of ultraviolet and NMR studies which indicate absence of an acidic N-H function. Compound IV and its pyridine analog, tetrazolo[1,5-*a*]pyridine (24), absorb at 271 and 258 mμ, respectively in both water and dilute alkali, whereas the pyridine analog of V, 1*H*-*v*-triazolo-[4,5-*b*]pyridine (25), exhibited a bathochromic shift from 280 mμ to 286 mμ under the same conditions. The results of NMR spectroscopy in deuteriochloroform are compiled in Table II. For comparative purposes the corresponding values for pyrrolo-[1,2-*a*]pyrazine (VI) (26) are also listed.

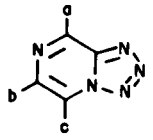
TABLE I

Compound	Medium	Temp., °C	$t_{1/2}$
Fluoropyrazine	0.01*N* NaOH	R.T. (d)	*ca.* 7 days
	1.07*N* NaOH	26.0	42.7 minutes
	0.01*N* HCl	R.T.	stable (a)
	6 *N* HCl	R.T.	*ca.* 4 days
Chloropyrazine	1.07*N* NaOH	R.T.	*ca.* 19 days
Iodopyrazine	1.07*N* NaOH	R.T.	stable (b)
2-Fluoropyridine	0.01*N* NaOH	R.T.	stable (a)
	0.01*N* HCl	R.T.	stable (a)
	1.07*N* NaOH	R.T.	stable (c)
2-Fluoroquinoxaline	0.01*N* NaOH	26.0	42.5 minutes

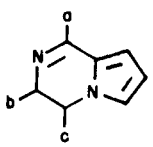
(a) No significant change. (b) 12% Change in 18 days. (c) Less than 5% change in 4 days. (d) Room temperature (22-26°).

TABLE II

NMR Spectra



IV



VI

	IV	VI
a	9.64 (a)	8.91 (a)
b	8.36	7.58
c	8.83	7.89
$J_{a,c}$	1.6 (b)	1.55 (b)
$J_{a,b}$	< 0.5	--
$J_{b,c}$	4.7	5.5

(a) In ppm relative to TMS. (b) In c.p.s.

EXPERIMENTAL

All the melting points were determined in glass capillaries and are corrected. Ultraviolet measurements were made with the Perkin-Elmer 202 ultraviolet-visible spectrophotometer. NMR spectra were obtained with a Varian A-60 spectrometer in carbon tetrachloride or deuteriochloroform with tetramethylsilane (TMS) as internal standard. Elemental analyses were performed at the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Fluoropyrazine (I).

Procedure A (via Aminopyrazine).

The diazotization of aminopyrazine (27) was conducted in a thin-walled (500 ml.) polyethylene beaker equipped with an efficient magnetic or mechanical stirrer and a glass thermometer sheathed in a brass tube containing a small pool of mercury for efficient heat transfer. Aminopyrazine (25 g., 0.26 mole) and 0.5 g. of copper powder were added to 150 ml. of 40% fluoroboric acid (28) and the mixture was stirred briefly at room temperature. After cooling to -5 to 0° in a methanol-Dry Ice bath (crystals formed at 10°), powdered sodium nitrite (21 g., 0.31 mole) was added in small portions over a period of 60 to 80 minutes at -5 to 0°. Efficient mixing was impeded by the formation of crystalline diazonium fluoroborate as well as by foaming due to evolution of nitrogen. Addition of small portions of ether and manual stirring with a copper rod was necessary during the first 30 minutes. Thereafter, the suspension became considerably thinner and permitted faster addition of sodium nitrite. The light brown reaction mixture was stirred at 0° for 15 minutes and warmed to 20° over a period of 30 minutes to complete decomposition of the diazonium salt.

The reaction mixture was carefully neutralized to a *p*H of 5-6 with solid sodium carbonate at 5-10° and extracted twice with 50 ml. and six times with 30 ml. portions of absolute ether. Clear separations of layers were achieved despite the presence of a dark brown precipitate in the aqueous phase. The combined ether layers were dried by stirring for 2 hours over 20 g. of anhydrous magnesium sulfate.

Removal of the solvent through a 20-inch Vigreux column gave a light brown concentrate which was fractionally distilled from 2 ml. of bis (2-methoxyethyl) ether (b.p. 161°) which served as a chaser. The fraction boiling between 95° and 130° (8-9 g.) was refractionated to give 5.7-6.5 g. (22-25% of theory) of fluoropyrazine as a mobile, colorless liquid, b.p. 108-109.5°/atm., $n_D^{22.5}$ = 1.4670.

Ultraviolet spectrum: λ max (95% ethanol): 261 and 265 mμ (ε, 5,300), 295 mμ (shoulder).

Anal. Calcd. for $C_4H_3N_2F$: C, 48.98; H, 3.08; N, 28.56; F, 19.38. Found: C, 48.86; H, 3.17; N, 28.44; F, 19.21.

Procedure B (via Chloropyrazine).

Finely powdered potassium fluoride dihydrate (2.0 g., 21 mmoles) was suspended in 30 ml. of dimethyl sulfoxide and dehydrated by distilling part of the solvent (15 ml.) through a short, air-cooled condenser until the vapor temperature became constant at 191°. After cooling, 2.05 g. of chloropyrazine (18 mmoles) (2) was added and the mixture refluxed gently with stirring for 2 hours. Distillation through a 5-inch Vigreux column yielded a fraction of boiling range of 105-160°/atm. It was transferred with absolute ether to a micro still equipped with a 5-inch Vigreux column and fractionated. The fraction boiling at 107-110°/atm., $n_D^{24.3}$ = 1.4620, weighed 1.00 g. (57% of theory) and consisted of nearly pure fluoropyrazine containing a small amount of water and less than 5% chloropyrazine by infrared spectroscopy.

Hydrolysis of I.

Fluoropyrazine (0.55 g., 5.6 mmoles) was dissolved in 16 ml. of 1.07*N* sodium hydroxide (17 mmoles) and allowed to stand at room temperature for 3 days. The faintly yellow solution was neutralized to a *p*H of 5-6 with concentrated hydrochloric acid and evaporated to dryness *in vacuo*. The white residue was extracted twice with 50 ml. of hot acetone-methanol (4:1). Evaporation of the filtrates *in vacuo* yielded 0.60 g. of tan-colored solids, m.p. 183.5-184.5° dec. Sublimation at 90-130°/0.3 mm. gave 0.500 g. of white sublimate (93% of theory), m.p. 187-188° dec.; pyrazinol: m.p. 187.5-188.5° dec. (29); mixture melting point, undepressed.

The U. V. spectrum in 95% ethanol, λ max 223 and 319 mμ was identical with that of authentic pyrazinol.

Ammonolysis of I.

Fluoropyrazine (0.55 g., 5.6 mmoles) was mixed with 5 ml. of concentrated aqueous ammonia (28%) and the homogeneous solution allowed to stand at room temperature for 3 days until the ultraviolet peak at 264 mμ had disappeared. After evaporation *in vacuo* to dryness, the residue was extracted with hot acetone (50 ml.) and the filtrate evaporated to dryness *in vacuo*.

Sublimation of the residue at 50-80°/0.2 mm. gave 0.373 g. (70%) faintly yellow crystals, m.p. 116-118°; aminopyrazine: lit. (27) m.p. 118-120°; mixture melting point 116.5-119°.

The U. V. spectra of the sublimate and of aminopyrazine were identical (λ max 230 and 328 mμ in 0.1*N* sodium hydroxide).

No significant reaction occurred between fluoropyrazine and methanolic ammonia on standing at room temperature for 6 hours, or between fluoropyrazine and anhydrous ammonia upon refluxing in benzene for 2 hours.

2-Fluoroquinoxaline (II).

2-Aminoquinoxaline (14.7 g., 0.10 mole, m.p. 155-156°) (30) was added to 250 ml. of 40% fluoroboric acid in the 500 ml. reaction vessel used for fluoropyrazine. The deep brown solution was stirred until crystallization was complete resulting in a heavy stirrable suspension. After cooling to -5 to 0° in a methanol-Dry Ice bath, solid sodium nitrite (7.2 g., 0.10 mole) was added in small portions along with small quantities of ether as needed to control foaming. The addition of sodium nitrite required 20-30 minutes. After adding 0.1 g. of copper powder the reaction mixture was gradually warmed to 23° over a period of 20 minutes and held at this temperature for 5 minutes until the yellow precipitate dissolved. Ice water (1 liter) was added and the mixture was extracted with chloroform (4 x 50 ml.), without prior neutralization. After washing with ice water (4 x 75 ml.), the chloroform layer was dried over 25 g. of anhydrous magnesium sulfate by stirring for 0.5 hour in an ice bath. Concentration of the filtrate (*ca.* 300 ml.) *in vacuo* to approximately 25 ml. caused formation of a yellow precipitate of 2-quinoxalinol which was filtered off after dilution with one volume of ether. The filtrate was concentrated *in vacuo* and fractionated. The fraction of boiling range 95-97°/11 mm. totalled 4.53 g. (30% yield). The central fraction, boiling point 96-97.5°/11 mm. and $n_D^{22.5}$ = 1.5883, was submitted for analysis.

Ultraviolet spectrum: λ max (95% ethanol): 210 (9,100), 235 (19,300), 313 (4,900), 238, 325 mμ (shoulder).

Anal. Calcd. for $C_8H_5N_2F$: C, 64.85; H, 3.40; N, 18.91; F, 12.83. Found: C, 64.78; H, 3.40; N, 18.90; F, 12.95.

Hydrolysis of II.

2-Fluoroquinoxaline (0.46 g., 3.1 mmoles) was treated with 9.0 ml. of 1.07*N* sodium hydroxide (9.6 mmoles). The mixture was shaken for 5-7 minutes until a homogeneous solution was obtained and allowed to stand at room temperature for 3 days. The light yellow solution was neutralized (*p*H 5-6) with 1*N* hydrochloric acid. The resultant white precipitate was filtered and washed with three portions of ice water. After drying at 120° for 1 hour, the 2-quinoxalinol weighed 0.444 g. (97%) and melted at 270-271° dec., lit. (31) m.p. 271°.

Methylaminopyrazine.

Fluoropyrazine (0.57 g., 5.8 mmoles) in 5 ml. of methanol was treated with 0.80 ml. of 40% aqueous methylamine. After standing at room temperature for 3 days, the reaction mixture was partly evaporated and diluted with 10 ml. of water. The product was extracted with chloroform (5 x 10 ml.). Drying with anhydrous sodium sulfate and evaporation *in vacuo* gave a crystalline residue which was sublimed at 20-40°/0.2 mm. The hydroscopic sublimate weighed 0.558 g. (88%) after drying at room temperature over phosphorus pentoxide

and melted at 49-50°; m.p. of picrate (from 95% ethanol): 177-177.5°; lit. (21) m.p. 49-50°, picrate: 180-181° corr.

Piperidinopyrazine.

Fluoropyrazine (0.51 g., 5.2 mmoles), methanol (2 ml.) and piperidine (0.88 g., 10.4 mmoles) were mixed and kept at room temperature for 4 days. Evaporation *in vacuo* yielded an oily residue which was dissolved in 25 ml. of water and acidified (*p*H 2-3) with hydrochloric acid. The product was extracted with chloroform (5 x 15 ml.), washed once with aqueous sodium bicarbonate and dried over sodium sulfate. The residue obtained by evaporation was sublimed at 35-45°/0.2 mm. The sublimate, dried over phosphorus pentoxide *in vacuo* at room temperature, weighed 0.804 g. (95%) and melted at 39-40°; m.p. of picrate (from 95% ethanol): 116-117°.

Anal. Calcd. for $C_9H_{13}N_3$: C, 66.22; H, 8.03; N, 25.75. Found: C, 66.27; H, 7.97; N, 25.72.

Benzylaminopyrazine.

Fluoropyrazine (0.50 g., 5.1 mmoles), methanol (5 ml.) and benzylamine (1.2 g., 11.0 mmoles) were stored at room temperature for 3 days. The mixture was evaporated *in vacuo* and extracted into ether (5 x 15 ml.) from a slightly acidic aqueous solution (*p*H 2-3). The ether layer was washed once with aqueous sodium bicarbonate, dried over sodium sulfate and evaporated. Sublimation of the residue at 90-130°/0.3-0.5 mm. (as a melt) yielded 0.700 g. (74%) of benzylaminopyrazine m.p. 71-71.5°, lit. (32) m.p. 67-68°; m.p. of picrate (immediate precipitation from 95% ethanol): 139.7-140°, lit. (32) m.p.: 139.8-141.2° corr.

Anilinopyrazine.

Fluoropyrazine (0.47 g., 4.8 mmoles) and 1.8 ml. (20 mmoles) of aniline were heated in a sealed tube at 130-135° for 9 hours. The dark brown, semi-crystalline reaction mixture was treated with ether (50 ml.), washed twice with water (15 ml.) and once with aqueous sodium bicarbonate. The ether layer was dried with anhydrous sodium sulfate and evaporated. The oily residue deposited crystals on standing and was diluted with cyclohexane-hexane. Filtration afforded 0.161 g. (20%) of light gray crystals, m.p. 135-136°.

For analysis, a portion was sublimed and recrystallized from methylene chloride-cyclohexane to yield colorless, granular crystals, m.p. 135.5-136.2°.

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.12; H, 4.96; N, 24.98.

In a preliminary experiment a slightly higher yield (24%) was obtained with a shorter reaction time (3 hours) and the use of two moles of aniline.

Pyrazinesulfonic Acid (Sodium Salt).

Fluoropyrazine (0.51 g., 5.2 mmoles) and 0.96 g. (7.6 mmoles) anhydrous sodium sulfite in 5 ml. of water were refluxed with stirring for 2 hours until the disappearance of the azeotrope. The reaction mixture was evaporated to dryness *in vacuo* and extracted twice with 50 ml. portions of hot 95% ethanol. Evaporation to *ca.* 25 ml. gave a first crop of white crystals weighing 0.71 g. (68% as the monohydrate), m.p. 298-300° dec. lit. (33) m.p. 295° dec.

Ultraviolet spectrum: λ max (water): 204 (7,400), 267 (8,200), 274 (shoulder), 309 mμ (840, broad). The ultraviolet spectrum is identical to the one reported for this compound by Weintraub (34).

Tetrazolo[1,5-*a*]pyrazine.

A mixture of 1.0 g. of fluoropyrazine (10.2 mmoles) and 1.0 g. of powdered sodium azide (30 mmoles) in 10 ml. of 80% ethanol was refluxed with vigorous stirring for 8 hours. Evaporation to dryness *in vacuo* gave a residue which was extracted with 70 ml. of hot acetone. Evaporation of the solvent and sublimation of the residue at 80-100°/0.2-0.3 mm. afforded 0.464 g. (37.5%) of tan-colored crystals, m.p. 89.5-91°. Recrystallization from methylene chloride-cyclohexane yielded 0.443 g. (36%) of white crystals, m.p. 90.8-91.5°.

Ultraviolet spectrum: λ max (water): 203 (12,000), 270 mμ (4,500, broad); λ max (0.01*N* sodium hydroxide): 211 (4,600), 271 mμ (4,500).

Anal. Calcd. for $C_4H_3N_5$: C, 39.67; H, 2.50; N, 57.82. Found: C, 39.83; H, 2.71; N, 57.55.

Kinetic Measurements.

All the hydrolyses were conducted under pseudo first-order conditions in the presence of a minimum of a 100 fold excess of reagent. The rate constants and half-lives were computed from spectrophotometric measurements at the wave length of the corresponding hydroxy derivative, 317 mμ for pyrazinol and 352 mμ for 2-quinoxalinol, and in some instances from the rate of disappearance of the substrate. Hydrolysis of fluoropyrazine in 1.07*N* sodium hydroxide at 26.00 ± 0.03° gave half-lives of 42.7 ± 1.6 minutes 42.7 ± 1.1 minute in duplicate experiments. Similar values, 42.2 ± 0.7 minutes and 42.8 ± 0.4 minute were obtained for 2-fluoroquinoxaline in 0.01*N* sodium hydroxide at 26.00 ± 0.03° over a range of four half-lives. The remainder of the hydrolyses were much slower and were conducted at room temperature. The data are summarized in Table I.

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