Oxidation of Fluorenamines and Preparation of 2,2′- and 4,4′-Azofluorene[1]

YUL YOST

Laboratory for Cancer Research, Veterans Administration Hospital and Department of Biochemistry, University of Minnesota, Minneapolis, Minnesota

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Fluorenylhydroxamic acids, particularly those obtained from 2-nitrofluorene, are strong carcinogens. The latter is commercially available. Certain derivatives of 1- and 3-nitrofluorene have recently been found to be carcinogens[2] as well. 1-, 3-, and 4-nitrofluorene[3] are best prepared (69–80%) by oxidation of the respective amines with *m*-chloroperbenzoic acid.

2,2′-Azoxyfluorene[4] and 2,2′-azofluorene are spectroscopically barely distinguishable. The reported identity of 2,2′-azoxyfluorene, isolated from rat liver incubated with N-(fluoren-2-yl)acetohydroxamic acid, is therefore questionable.[5]

TABLE I

OXIDATION OF FLUORENAMINES WITH *m*-CPB ACID

Fluorenamine used	Mole ratio (acid:amine)	Reflux time, min	Product[a]	Mp, °C	% yield
1	5	15	Nitrofluorene	104–106	69
2	3.05	15	Nitrofluorene	154–157	81
3	5	15	Nitrofluorene	99–105	72
4	2	15	Nitrosofluorene	110–112	80
4	5	90	Nitrofluorene	72–75	80

[a] All products were purified as described for 1-nitrofluorene.

Experimental Section[6]

1-Nitrofluorene (Table I).—Fluoren-1-amine[3] (2.00 g, 0.011 mole) in $CHCl_3$ (40 ml) was added to a cold solution of *m*-chloroperbenzoic (*m*-CPB) acid (0.0350 *M* in $CHCl_3$; 0.157 l., 0.055 mole). The reaction mixture was stirred at 0° for 15 min, then brought to room temperature with lukewarm H_2O, kept there for 30 min, and finally refluxed for 15 min. The organic phase was extracted with 0.5 *N* NaOH (two 60-ml portions), washed (H_2O), and dried ($MgSO_4$) and the solvent was evaporated. The residue was applied on an alumina (50 g) column packed with hexane and chromatographed with a 10% (v/v) solution of CH_2Cl_2 in hexane. The per cent of CH_2Cl_2 was increased as the chromatography proceeded. The eluate of initial fractions was concentrated and cooled and the product was collected by filtration (69%).

2-Nitrosofluorene.—A simplified method of a previous one was used.[7] The undried, filtered, and washed paste of 2-fluorenylhydroxylamine, obtained from partial reduction of 6.00 g (0.0286 mole) of 2-nitrofluorene with H_2S in the presence of NH_3, was dissolved in cold DMF (600 ml).[8,9] Cold aqueous 0.43 *N* ferric ammonium sulfate (100 ml, 0.043 mole) was poured into the DMF solution. An orange precipitate resulted. The reaction mixture was stirred under N_2 for 15 min. The orange precipitate (2,2′-azoxyfluorene, determined by elemental analysis and uv spectrum; mp 262° dec, lit.[4] 279°) was removed; ice-cold H_2O (1300 ml) was added to the filtrate. The resulting green precipitated product was collected by filtration, washed (cold H_2O), and dried *in vacuo* (2.60 g, 47%), mp 72–78°, lit.[7] 77–79°. It had a uv spectrum identical with that of authentic compound. Purer product (mp 78–79°) was obtained by recrystallizing the crude product from hexane.

2,2′-Azofluorene.—Fluoren-2-amine (181 mg, 1.00 mmole) in AcOH (6 ml) was added to 2-nitrosofluorene (195 mg, 1.00 mmole) in AcOH (8 ml), and then let stand at room temperature.[10] The next day the orange precipitate was collected and washed with EtOH (250 mg, 70%); mp 260° dec. Analytically pure sample was obtained by recrystallization of the crude product from boiling C_6H_6 to give orange prisms: mp 262° dec; $\lambda_{max}^{CHCl_3}$ 252, 262 infl, 384 mμ; mixture melting point with an analytical sample of 2,2′-azoxyfluorene (mp 265° dec, lit.[4] 279°) was undepressed. *Anal.* ($C_{26}H_{18}N_2$) C, H, N.

The identity of the compound was further established by reducing it with Zn in AcOH to fluoren-2-amine (45%) and 2-fluorenylacetamide (23%).

4,4′-Azofluorene.—4-Nitrosofluorene[3] (195 mg, 1.00 mmole) in $CHCl_3$ (3 ml) was added to a solution of fluoren-4-amine[3] (181 mg, 1.00 mmole) in AcOH (7 ml).[10] The reaction flask was heated on a steam bath for 1 hr. The product settled as reddish brown crystals after the reaction mixture stood at room temperature for 1 week; it was collected and recrystallized from C_6H_6 (45%); mp 261° dec; $\lambda_{max}^{CHCl_3}$ 257, 265 infl, 343 mμ. *Anal.* ($C_{26}H_{18}N_2$) C, H, N.

(1) This work was supported in part by U. S. Public Health Service Research Grant CA-20571-14, and the excellent technical assistance of Charles Muscoplat is acknowledged.

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(6) Melting points were taken with a Fisher-Johns apparatus and are uncorrected. Uv spectra were recorded (in mμ) with a Beckman DK-2 spectrophotometer. The fluorenamines were obtained from the respective aminofluorenones and 3-nitrofluoren-9-one which were purchased from Aldrich Chemical Co., Inc., Milwaukee, Wis. The *m*-chloroperbenzoic (*m*-CPB) acid was obtained from Organic/Inorganic Chemical Co., Sun Valley, Calif.

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Stable Oxaziridines[1]

J. CHAKRAVARTY AND PRICE TRUITT

Department of Chemistry, North Texas State University, Denton, Texas 76203

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Although oxaziridines have been known for several years[2] and a variety of methods have been utilized for their synthesis,[3] we were unable to find a report on their physiological activities. Thus we decided to prepare a number of oxaziridines (Table I) in order to compare their physiological activities with particular reference to antitumor activity.

(1) This investigation was supported by Public Health Service Research Grant No. CA10530 from the National Cancer Institute and a Faculty Grant from North Texas State University.

(2) W. D. Emmons, *J. Am. Chem. Soc.*, **78**, 6208 (1956); L. Horner and E. Jurgens, *Ber.*, **90**, 2184 (1957); H. Krimm, *ibid.*, **91**, 1057 (1958).

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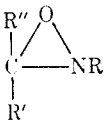
TABLE I

OXAZIRIDINES



R	R′	R″	Yield, %	Bp (mm) or mp, °C	Formula[a,b]
C_6H_{11}	H	*m*-ClC_6H_4	99	41	$C_{13}H_{16}ClNO$
C_6H_{11}	H	*p*-ClC_6H_4	99.2	68–69	$C_{13}H_{16}ClNO$
C_6H_{11}	H	*o*-$NO_2C_6H_4$	95.9	58–59	$C_{13}H_{16}N_2O_3$
C_6H_{11}	H	*m*-$NO_2C_6H_4$	99.2	64–65	$C_{13}H_{16}N_2O_3$
C_6H_{11}	H	*p*-$NO_2C_6H_4$	98.8	72–73	$C_{13}H_{16}N_2O_3$
C_6H_{11}	H	3,4-$(CH_3O)_2C_6H_3$	98.4	Gum	$C_{15}H_{21}NO_3$
t-C_4H_9	H	*m*-ClC_6H_4	98	45–46	$C_{11}H_{14}ClNO$
t-C_4H_9	H	*p*-ClC_6H_4	98.6	67	$C_{11}H_{14}ClNO$
t-C_4H_9	H	*o*-$NO_2C_6H_4$	98.7	35–36	$C_{11}H_{14}N_2O_3$
t-C_4H_9	H	*m*-$NO_2C_6H_4$	97.5	46–47	$C_{11}H_{14}N_2O_3$
t-C_4H_9	H	3,4-$(CH_3O)_2C_6H_3$	95.4	60	$C_{13}H_{19}NO_3$
i-C_3H_7	Tetramethylene		48	58–60 (10)	$C_8H_{15}NO$
sec-C_4H_9	H	C_6H_5	93.7	82–83 (1.5)	$C_{11}H_{15}NO$

[a] These compounds were titrated with KI to determine active oxygen and all gave 97–99.3% of the calculated values. All compounds were analyzed for C, H, N, and the analytical results obtained were within ±0.4% of the theoretical values. [b] We wish to thank Ed Hoff for C, H, N analyses.

Experimental Section

The oxaziridines were prepared by the peracetic acid[2] or *m*-chloroperbenzoic acid[4] oxidation of the corresponding imines. The oxaziridines were isolated by distillation at reduced pressure and in some cases additional purification was obtained by chromatographing with a neutral alumina column.

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Possible Anticonvulsant Thiazolo[3,2-*a*]benzimidazole Mannich Bases. XI[1]

J. M. SINGH[2]

School of Chemistry, Meerut College, Meerut, India

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In view of the potent pharmacodynamic activity[3] of a large number of thiazole Mannich bases, additional thiazolo[3,2-*a*]benzimidazole Mannich bases were synthesized. These compounds have been tested for anticonvulsant activity (Table I).

Experimental Section

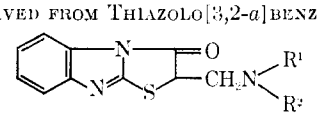
Thiazolo[3,2-*a*]benzimidazol-3(2H)-one.—2-Carbethoxymethylthiobenzimidazole[4] (5 g) in *o*-$PhCl_2$ (20 ml) was refluxed for 1 hr while removing EtOH. The mixture became quite dark; colored crystals (1 g) separated and were recrystallized (EtOH), mp 179–180°.

Diethylaminothiazolo[3,2-*a*]benzimidazol-3(2H)-one.—A mixture of thiazolo[3,2-*a*]benzimidazol-3(2H)-one (2 g), Et_2NH (2 ml), AcOH (10 ml), and CH_2O (2 ml) was heated on a steam bath for 7 hr. After cooling, H_2O (20 ml) was added and the solution was neutralized with saturated aqueous K_2CO_3. The base was filtered, washed (H_2O), and recrystallized (EtOH), yield 42%, mp 210°. *Anal.* ($C_{14}H_{17}NSO$) N, S.

The above procedure was followed to prepare the other compounds.

TABLE I

MANNICH BASES DERIVED FROM THIAZOLO[3,2-*a*]BENZIMIDAZOL-3(2H)-ONE[a]



No.	$N(R_1R_2)$	Formula	Mp, °C	Yield, %	Activity[b]	LD_{50} (toxicity), mg/kg
1	Et_2N	$C_{14}H_{17}N_3SO$	210	42	++	250
2	Me_2N	$C_{12}H_{17}N_3SO$	190	45	+	390
3	Ph_2N	$C_{22}H_{17}N_3SO$	175	50	+++	350
4	PhNEt	$C_{18}H_{17}N_3SO$	250	40	++	290
5	*n*-Pr_2N	$C_{16}H_{21}N_3SO$	240	45	++	370
6	*n*-Bu_2N	$C_{18}H_{25}N_3SO$	250	50	+++	400
7	*sec*-Bu_2N	$C_{18}H_{25}N_3SO$	210	45	+++	500
8	Piperidino	$C_{15}H_{17}N_3SO$	215	40	++++	450
9	Morpholino	$C_{14}H_{15}N_3SO_2$	230	41	+++++	480

[a] All new compounds were analyzed for N and S; the analytical values were within ±0.4% of the calculated values. [b] Mice were used for the experiments for anticonvulsant activity following the method by T. J. Putnam and H. H. Merritt, *Science*, **85**, 525 (1937). +++++ = convulsive threshold elevated more than 60 mA, ++++ raised by 60 mA, +++ = raised by 40 mA, ++ = raised by 15–20 mA, and + = raised by 10–15 mA, 2 hr after treatment.

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(2) Address inquiries to Defence Science Laboratory, Delhi-6, India.

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