gave the amide, mp 268–270°. Recrystallization (EtOH) raised the melting point to 271–272°. *Anal.* ($C_{16}H_{13}NO_4S$) C, H, N.

6-Mesyl-2-fluorenamine (VI).—A mixture of 3 g of 6-mesyl-2-nitro-9-oxofluorene, 20 ml diethylene glycol, and 10 ml of 85% $N_2H_4 \cdot H_2O$ was heated under reflux for 2 hr and then without a condenser until the temperature of the mixture rose to 205°, after which refluxing was resumed for 2 more hr. When the mixture had cooled, it was poured into 100 ml of water to form a white precipitate, mp 181–184°. Two recrystallizaions (EtOH) gave an analytical sample, mp 184–185°. *Anal.* ($C_{14}H_{13}NO_2S$) C, H.

N-2-(6-Mesylfluorenyl)acetamide (VIII).—Acetylation of the foregoing amine, followed by crystallization (EtOH), gave an analytical sample, mp 237–238°. *Anal.* ($C_{16}H_{15}NO_3S$) N, S.

Derivatives of Fluorene. XXVIII.[1a,b] New Thiofluorenes Related to Metabolism of the Carcinogen N-2-Fluorenylacetamide. III[1c,d]

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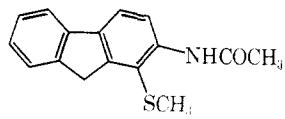
The formation of N-2-(3-methylthiofluorenyl)acetamide as a product of the *in vitro* reaction of esters of the carcinogen N-hydroxy-N-2-fluorenylacetamide with methionine under physiological conditions,[2] and the liberation of this methylthio derivative from the liver protein of rats administered the same carcinogen,[3a] led to our investigation of the syntheses of methylthiofluorene derivatives.[1c] The synthesis of the 3-methylthio derivative has been reported.[1c] This paper reports the syntheses of 1-, 5-, and 7-methylthio-2-acetamidofluorene (**1**, **2**, **3**) and their corresponding



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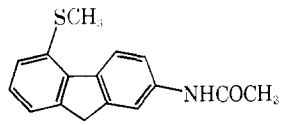

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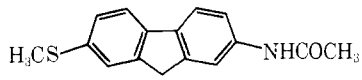
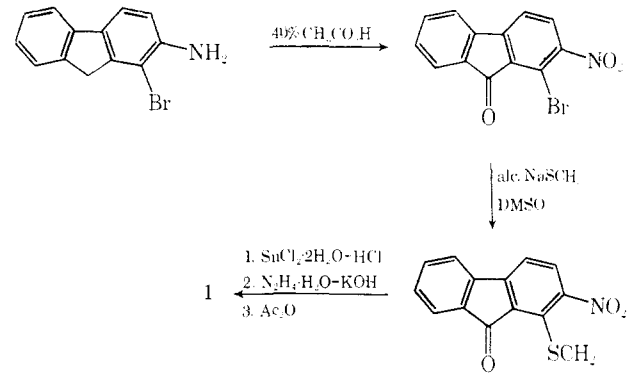


3

amines. These compounds were synthesized to facilitate the search for these derivatives as possible additional products of the reaction of these biologically important esters of N-hydroxy-N-2-fluorenylacetamide with methionine derivatives *in vitro* and *in vivo*. With these compounds as reference standards, DeBaun, Miller, and Miller (cited in ref 3b) have now identified N-2-(1-methylthiofluorenyl)acetamide as one of the products of the *in vitro* and *in vivo* reactions of esters of N-hydroxy-N-2-fluorenylacetamide with methionine; the 5- and 7-methylthio derivatives have not been detected in these reactions.

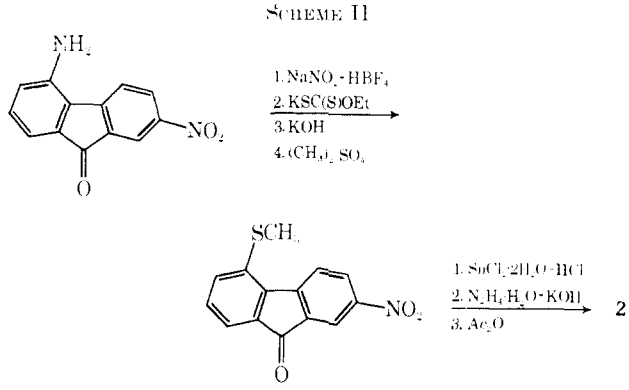
In the synthesis of **1**, 1-bromofluoren-2-amine[4] was oxidized with 40% peracetic acid to 1-bromo-2-nitro-9-oxofluorene (**4**). This was converted to the 1-methylthio derivative by treating **4** with $NaSCH_3$ in DMSO. Reduction of the 1-methylthio-2-nitro compound in two steps gave 1-methylthio-9-oxofluoren-2-amine (**5**) and 1-methylthiofluoren-2-amine (**6**). The latter was acetylated to give **1** (Scheme I).

SCHEME I



Attempts to prepare **2** and **3** by starting with 2-nitrofluoren-5-amine and 7-nitrofluoren-2-amine, respectively, were unsuccessful. However, **2** was successfully synthesized by starting with 2-nitro-9-oxofluoren-5-amine.[5] A diazonium fluoroborate was prepared from this amine and the diazonium salt was converted into a xanthate which, upon hydrolysis and methylation, gave 5-methylthio-2-nitro-9-oxofluorene. This nitro compound was first reduced to 5-methylthio-9-oxofluoren-2-amine (**7**) then to 5-methylthiofluoren-2-amine (**8**). Acetylation of the latter gave **2** (Scheme II).

SCHEME II



Preparation of **3** was accomplished in a similar manner from N-2-(7-aminofluorenyl)acetamide,[6] with the $NHCOCH_3$ group already in place. Acid hydrolysis of **3** gave us the amine **9**.

(1) (a) Paper XXV: M. J. Namkung and T. L. Fletcher, *Can. J. Chem.*, **45**, 2569 (1967). (b) Supported in part by a grant (CA-01744) from the National Cancer Institute, National Institutes of Health, and in part by Research Career Development Award 5-K3-CA-14,991 (T.L.F.). (c) Thiofluorenes. I: T. L. Fletcher, M. J. Namkung, and H.-L. Pan, *J. Med. Chem.*, **10**, 936 (1967). (d) Paper XXVII (Thiofluorenes. II): M. J. Namkung and T. L. Fletcher, *ibid.*, **11**, 1235 (1968).

(2) P. D. Lotlikar, J. D. Scribner, J. A. Miller, and E. C. Miller, *Life Sci.*, **5**, 1263 (1966).

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(4) T. L. Fletcher, M. J. Namkung, and H.-L. Pan, *Chem. Ind. (London)*, 660 (1957).

(5) F. J. Moore and E. H. Huntress, *J. Am. Chem. Soc.*, **49**, 1324 (1927).

(6) T. L. Fletcher and M. J. Namkung, *J. Org. Chem.*, **23**, 680 (1958).

Experimental Section[7]

1-Bromo-2-nitro-9-oxofluorene (**4**).—1-Bromofluoren-2-amine[4] (15 g, 0.057 mole) was added in small amounts to rapidly stirred cold 40% AcO_2H (300 ml) over a period of 20 min. The resulting suspension was slowly heated (*caution!*) to refluxing, refluxed continuously with stirring for 3 hr, and cooled. After water dilution the precipitate was dissolved in boiling AcOH. To the stirred boiling solution $Na_2Cr_2O_7 \cdot 2H_2O$ (50 g) was added portionwise within 15 min. Boiling was continued for 30 min and the mixture was cooled. The product was triturated in H_2O and isolated giving 8.5 g (49%). Sublimation at 145–155° (bath) (0.01 mm) gave a sample melting at 221–222°. *Anal.* ($C_{13}H_6BrNO_3$) C, H, Br, N.

1-Methylthio-9-oxofluoren-2-amine (**5**).—To a stirred suspension of **4** (1.4 g) in DMSO (75 ml) a fresh[1c] 10% solution of $NaSCH_3$ in absolute EtOH (3.4 ml, 1 equiv) was added dropwise over a 45-min period. The mixture was continuously stirred at ambient temperature for 46 hr then poured into water containing a few milliliters of concentrated HCl. The product, **1-methylthio-2-nitro-9-oxofluorene,** was chromatographed in C_6H_6 (alumina), giving 0.65 g, mp 155–159°. Reduction with $SnCl_2 \cdot 2H_2O$ (6 g) and concentrated HCl (30 ml) gave a product which was chromatographed twice (alumina, C_6H_6) giving 0.3 g of **5**, mp 171–172°. *Anal.* ($C_{14}H_{11}NOS$) N, S.

1-Methylthiofluoren-2-amine (**6**).—A mixture of **5** (0.24 g, 1 mmole), 99–100% hydrazine hydrate (2 ml), KOH (0.5 g), and 2,2'-oxydiethanol (25 ml) was gently refluxed for 0.5 hr, diluted (H_2O), and refrigerated overnight. The product was isolated giving 0.2 g (89%), mp 78–79°. *Anal.* ($C_{14}H_{13}NS$) N.

N-2-(1-Methylthiofluorenyl)acetamide (**1**).—Acetylation of **6** in AcOH with Ac_2O gave the product, mp 175–176°. *Anal.* ($C_{16}H_{15}NOS$) C, H, N, S.

5-Methylthio-9-oxofluoren-2-amine (**7**).—2-Nitro-9-oxofluorene-5-amine[5] (7.5 g) was diazotized in 32% H_2SO_4 (150 ml) at 5–10° with $NaNO_2$ (3.5 g); 50% HBF_4 (50 ml) was then added and the diazonium fluoroborate was collected, dried, and added in one portion to a stirred solution of potassium ethyl xanthate (50 g) in H_2O (100 ml). The mixture was heated gradually, with stirring, to 100° and cooled. The organic material was extracted (C_6H_6), washed (H_2O), dried (Drierite), and evaporated to a solid mass. This was mixed with a hot solution of KOH (1.7 g) in 95% EtOH (100 ml) and stirred at ambient temperature for 27 hr then filtered into 3 *N* HCl (1 l.). The solid residue was extracted three times with a hot solution of KOH (3 g) in 95% EtOH (50 ml) and filtered into the same 3 *N* HCl. The precipitated **5-mercapto-2-nitro-9-oxofluorene,** mp 123–126°, 3.6 g, was mixed with NaOH (2 g), H_2O (30 ml), and Me_2SO_4 (1.9 g). The mixture was shaken for 10 min and refluxed for 3 hr. After water dilution the methylthio derivative was mixed with $SnCl_2 \cdot 2H_2O$ (20 g) and concentrated HCl (80 ml). The mixture was boiled with stirring for 45 min and poured into 2 *N* NaOH (0.5 l.). The crude product (1.3 g) was chromatographed through alumina (C_6H_6) giving pure **7** as deep purple crystals, mp 124–126°. *Anal.* ($C_{14}H_{11}NOS$) C, H, N.

5-Methylthiofluoren-2-amine (**8**).—A mixture of **7** (0.15 g), 99–100% hydrazine hydrate (1 ml), KOH (0.15 g), and 2,2'-oxydiethanol (5 ml) was gently refluxed for 1 hr and diluted (H_2O). The oily precipitate, after refrigeration, was separated and recrystallized from 95% EtOH giving 0.1 g, mp 124–125°. *Anal.* ($C_{14}H_{13}NS$) N, S.

N-2-(5-Methylthiofluorenyl)acetamide (**2**).—Acetylation of **8** with Ac_2O in AcOH gave the product, mp 174–175.5°. *Anal.* ($C_{16}H_{15}NOS$) C, H, N, S.

N-2-(7-Methylthiofluorenyl)acetamide (**3**).—Diazotization of 5 g of N-2-(7-aminofluorenyl)acetamide[6] in 50% HBF_4 (20 ml) and DMSO (10 ml) with $NaNO_2$ (2.5 g) at <0° gave the diazonium fluoroborate, 7 g (98%), mp 148–150° dec. A slurry of the diazonium salt in H_2O (20 ml) was added with stirring to a solution of potassium ethyl xanthate (10 g) in H_2O (20 ml) at room temperature. The reaction mixture was gradually heated to 80° and cooled. The brown precipitate was collected, mixed with EtOH (30 ml) and an aqueous solution of KOH (3 g), boiled for 1 min, and cooled. MeI (5 ml) was added and the mixture was heated on a steam bath for 3 min and cooled. The precipitate was filtered giving 4.6 g (82%), mp 206–210°. This was dissolved (Me_2CO) and chromatographed (Me_2CO, acid-washed alumina); evaporation gave 3.4 g, mp 209–210°. *Anal.* ($C_{16}H_{15}NOS$) C, H, N, S.

7-Methylthiofluoren-2-amine (**9**).—A mixture of **3** (2 g), 95% EtOH (150 ml), and concentrated HCl (10 ml) was refluxed for 7 hr and then boiled with the condenser removed until a precipitate started to form. It was cooled, and the precipitate was collected, mixed with H_2O (50 ml), and basified with concentrated NH_4OH. The product was recrystallized from 95% EtOH (Darco) giving 1.3 g (77%), mp 156–157°. *Anal.* ($C_{14}H_{13}NS$) C, H, N, S.

Acknowledgment.—The authors are indebted to Miss Carol-Ann Cole for running the ir spectra and for the preparation of some of the starting materials.

(7) All melting points were taken on a Fisher-Johns block and are corrected to standards. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir spectra (KBr) (Beckman IR-5) were as expected. Analyses were done by Schwarzkopf Laboratories, Woodside, N. Y., and by A. Bernhardt, Mülheim (Ruhr).

2,4-Bis(aryloxy)pyrimidines as Antimicrobial Agents

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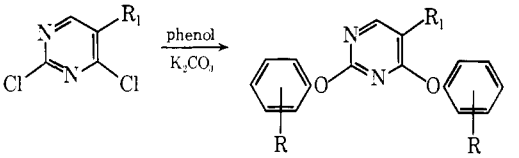
In our previous communications[1] it has been shown that 2,4-bis(arylamino)pyrimidines are potent antimicrobial agents. Encouraged by these findings we have prepared a series of 2,4-bis(aryloxy)pyrimidines (**1**). In this note the syntheses of I, R_1 = H or CH_3, by condensation of 2,4-dichloro-[2a] or 2,4-dichloro-5-methylpyrimidine[2b] with the appropriate phenolic compounds in the presence of anhydrous K_2CO_3 according to the method of Matsukawa and Shirakawa[3] are reported. These compounds have been tested against gram-positive and gram-negative bacteria and also against a pathogenic strain of yeast.



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The 5-methylbis(arylamino)-[1d] and 5-unsubstituted bis(arylamino)pyrimidines[1c] were found to be much more active than the corresponding bisaryloxypyrimidines. In contrast to bisarylaminopyrimidines, the biological activity of the bisaryloxypyrimidines is almost independent of the nature of the substituent in the phenyl ring. Methyl substitution in the 5 position of the pyrimidine ring does not alter significantly the inhibitory activity.

Experimental Section

General Method of Synthesis of 2,4-Bis(aryloxy)pyrimidines.—2,4-Dichloropyrimidine (0.01 mole) and phenol or substituted phenol (0.025 mole) were mixed as a melt and subsequently

(1) (a) D. Roy, S. Ghosh, and B. C. Guha, *J. Org. Chem.*, **25**, 1909 (1960); (b) *Arch. Biochem. Biophys.*, **92**, 366 (1961); (c) D. Ghosh, *J. Med. Chem.*, **9**, 424 (1966); (d) D. Ghosh and M. Mukherjee, *ibid.*, **10**, 974 (1967).

(2) (a) E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 1152 (1930); (b) O. Gerngross, *Ber.*, **38**, 3408 (1905).

(3) T. Matsukawa and K. Shirakawa, *J. Pharm. Soc. Japan*, **71**, 1313 (1951).