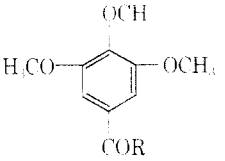
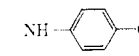
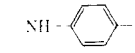
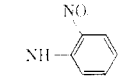
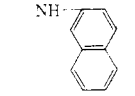
TABLE I

3,4,5-TRIMETHOXY-SUBSTITUTED BENZAMIDES[a]



Compd.	R	M.p., °C.	Formula	Yield, %	% calcd. C	H	N	% found C	H	N
I	$NHCOOC_2H_5$	120–123	$C_{13}H_{17}NO_6$	54	55.12	6.00	4.94	55.10	6.10	4.89
II		115–117	$C_{19}H_{21}NO_6$	62	63.50	5.84	3.89	63.16	5.83	3.79
III		180–183	$C_{16}H_{16}ClNO_4$	60	59.72	4.97	4.35	59.68	4.86	4.30
IV		145–147	$C_{15}H_{16}N_2O_6$	66	57.80	4.81	8.40	57.66	4.78	8.41
V		110–112	$C_{20}H_{19}NO_5$	60	71.21	5.63	4.15	71.28	5.56	4.08
VI		132–134	$C_{15}H_{21}NO_4$	58	64.51	7.53	5.01	64.01	7.46	5.00
VII	$NHCOC_2H_5$	184–186	$C_{13}H_{17}NO_5$	56	58.42	6.36	5.20	58.26	6.15	5.14

[a] All compounds except IV (yellow) were white.

stand overnight in refrigeration. The solvent was removed by distillation under reduced pressure. The solid residue was washed first with 5% HCl, then with 5% sodium carbonate, and then with distilled water repeatedly. The product was recrystallized from dilute methanol or ethanol.

N-Propionyl-3,4,5-trimethoxybenzamide (VII).—3,4,5-Trimethoxybenzamide (5 g.) in dry pyridine (20 ml.) was added dropwise to a cooled solution (below 10°) of propionyl chloride (2 ml.) in dry pyridine (20 ml.). The mixture was stirred at room temperature for about 1 hr. and then allowed to stand overnight. The mixture was warmed on a water bath for 20 min. and cooled, then poured into cold water (50 ml.) and filtered. The residue was washed repeatedly with distilled water and dried. The residue was recrystallized from benzene: yield, 56%; m.p. 184–186°.

Anal. Calcd. for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.36; N, 5.20. Found: C, 58.26; H, 6.15; N, 5.14.

1-(2-Deoxy-D-glucopyranosyl)-5-fluorocytosine[1]

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Received September 24, 1964

In view of the recent interest in 1-(2-deoxy-D-glucopyranosyl)-thymine as a "uridine phosphorylase" inhibitor[2] and of 2-deoxy-5-fluorocytidine as an antimetabolite[3] and antiviral agent,[4] it appeared of interest to synthesize the structurally related 1-(2-deoxy-D-glucopyranosyl)-5-fluorocytosine (III), in the hope that it might show one of the above physiological properties. The anomeric configuration of III is not known. However, in view of the physiological activity[2] of 1-(2-deoxy-D-glucopyranosyl)thymine (indicating β configuration), which was also prepared by the same method,[5] III may tentively be considered to be a β nucleoside.

(1) This work was supported in part by a research grant from the Michigan Cancer Foundation and in part by the research grant CA-08095-01 from the National Cancer Institute, Public Health Service.

(2) P. Langen and G. Etzold, *Biochem. Z.*, **339**, 190 (1963).

(3) R. Duschinsky, U. S. Patent 3,040,026 (1962).

(4) P. Calabreesi, R. W. McCollum, and A. D. Welch, *Nature*, **197**, 767 (1963).

(5) W. W. Zorbach and G. J. Durr, *J. Org. Chem.*, **27**, 1474 (1962).

Experimental[6]

2,4-Diethoxy-5-fluoropyrimidine (I).—This procedure follows the method of Hilbert and Johnson for the synthesis of 2,4-diethoxypyrimidines.[7] 2,4-Dichloro-5-fluoropyrimidine[3,8] (5.5 g., 0.033 mole) dissolved in 15 ml. of absolute ethanol was added to a solution of 4.7 g. (0.07 mole) of sodium ethoxide in 25 ml. of absolute ethanol. The mixture which became hot, was allowed to stand for 1 hr., filtered, and then was evaporated to dryness *in vacuo*. The residue was taken up in ether and water and, after washing with 30% aqueous NaOH, the ether layer was dried (Na_2SO_4) and filtered. The ether was removed *in vacuo* and the product was distilled, b.p. 92–93° (4 mm.), yielding 5.0 g. (82%) of I, m.p. 18–19°, $\lambda_{max}^{95\%\ EtOH}$ 269 mμ (log ε 3.72).

Anal. Calcd. for $C_8H_{11}FN_2O_2$: C, 51.60; H, 5.96; F, 10.20. Found: C, 51.78; H, 6.21; F, 9.88.

1-(3,4,6-Tri-O-*p*-nitrobenzoyl-2-deoxy-D-*arabino*-hexopyranosyl)-4-ethoxy-5-fluoro-2(1H)-pyrimidone (II).—This synthesis follows the classical method used by Hilbert and Jansen[9] in the synthesis of 1-(β-D-glucopyranosyl)cytosine. A mixture of 2.7 g. (4 mmoles) of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*arabino*-hexopyranosyl bromide[10] and 7.3 g. (39 mmoles) 2,4-diethoxy-5-fluoropyrimidine (I) was stirred *in vacuo* for 2 days at room temperature; initially, the bromo sugar dissolved with the evolution of ethyl bromide. The mixture was then triturated with 20 ml. of dry ether and filtered. The crude product was recrystallized from acetone, yielding 1.55 g. of II, m.p. 258.5–260°. An additional 0.2 g. of product was obtained from the mother liquors giving a total yield of 58%. The ultraviolet absorption spectra of the 1-substituted 4-ethoxy-5-fluoro-2-(1H)-pyrimidone was obscured by the absorption due to the *p*-nitrobenzoyl groups; $\lambda_{max}^{CH_2Cl_2}$ 262 mμ (log ε 5.66).

Anal. Calcd. for $C_{32}H_{26}FN_5O_{15}$: C, 52.75; H, 3.49; N, 9.32; F, 2.53. Found: C, 52.82; H, 3.56; N, 9.59; F, 2.81.

1-(2-Deoxy-D-glucopyranosyl)-5-fluorocytosine (III).—A mixture of 251 mg. (0.33 mmole) of II in 3.5 ml. of saturated methanolic ammonia was heated in a sealed tube at 100° for 3

(6) Melting points were determined using a Kofler hot stage. Ultraviolet spectra were recorded by a Bausch and Lomb Spectronic 505 spectrophotometer. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(7) G. E. Hilbert and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 1152 (1930).

(8) M. G. Biressi, M. Carrissimi, and F. Ravenna, *Gazz. chim. ital.*, **93**, 1268 (1963); L. D. Protsenko and Yu. I. Bogodist, *Zh. Obshch. Khim.*, **33**, 537 (1963).

(9) G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.*, **58**, 60 (1936).

(10) W. W. Zorbach and G. Pietsch, *Ann.*, **655**, 26 (1962).

days. At that time the solution was filtered and evaporated to dryness. The residue was partitioned between water and chloroform. The aqueous layer was evaporated to dryness *in vacuo* and the residue was crystallized from 2 ml. of water–3 ml. of absolute ethanol–20 ml. of ether yielding 70 mg. of product, as needles, m.p. 247–249° dec.; $\lambda_{max}^{0.1\ N\ HCl}$ 289 mμ (log ε 4.00), λ_{min} 244 mμ; $\lambda_{max}^{pH\ 7\ buffer}$ 274 mμ (log ε 3.93), λ_{min} 250 mμ; $\lambda_{max}^{0.1\ N\ NaOH}$ 278 mμ (log ε 3.84), λ_{min} 256 mμ; $[\alpha]^{27}D$ +30.6° (*c* 0.49, water).

Anal. Calcd. for $C_{10}H_{14}FN_3O_5$: C, 43.64; H, 5.13; N, 15.27; F, 6.91. Found: C, 43.44, 43.68; H, 5.15, 5.13; N, 15.01, 15.35; F, 7.13.

Some Bis(3-nitro- and 3-amino-4-alkoxy- and -4-aryloxyphenyl) Sulfones

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Received September 11, 1964

As part of a systematic study of the chemistry of bis(4-chloro-3-nitrophenyl) sulfone a group of bis(4-alkoxy- and 4-aryloxy-3-nitrophenyl) sulfones (Table I) and some corresponding 3-amino compounds (Table II) which have potential physiological interest have been synthesized.

Experimental

Bis(4-chlorophenyl) Sulfone.—This compound, m.p. 148–149°, was kindly contributed by the Stauffer Chemical Company. It was used for nitration without further purification.

Bis(4-chloro-3-nitrophenyl) Sulfone.—The above sulfone was nitrated in 97% yield by the method of Buehler and Masters.[1] After recrystallization from glacial acetic acid or dioxane it melted at 201–202° which agrees with the literature.[2]

Bis(4-alkoxy-3-nitrophenyl) Sulfones.—The first two members of this series have been described by Annaheim[3] and by Ullman and Korselt.[2] Annaheim prepared bis(4-methoxy-3-nitrophenyl) sulfone (I) and bis(4-ethoxy-3-nitrophenyl) sulfone (II) by nitration of the corresponding bis(4-alkoxyphenyl) sulfones. He reported the melting points of these compounds to be 214–215° and 192°, respectively. Ullman and Korselt prepared these compounds by treating bis(4-chloro-3-nitrophenyl) sulfone with the sodium alkoxides in the presence of the respective alcohol under pressure at 160° for 5 hr. They reported for I, m.p. 240°, and for II, m.p. 192°. Our preparation of I by the method described below melted at 216–217°.

We have found that the strenuous conditions used by Ullman and Korselt are not necessary to give satisfactory yields. The reaction is essentially complete at 65° in 15–60 min., except in the case of I which required 40 hr. at the temperature of refluxing methanol.

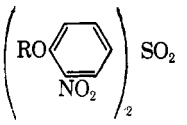
To a stirred solution of 1.6 g. (0.07 g.-atom) of sodium in 80 ml. of the anhydrous alcohol cooled to 40° was added 10 g. (0.026 mole) of bis(4-chloro-3-nitrophenyl) sulfone in portions. On warming, a mildly exothermic reaction occurred; the temperature was maintained at 65° for periods of 15–60 min. It was found that higher temperatures produced tarry products from which no crystalline product could be isolated. In the case of water-soluble alcohols, the reaction mixture was poured into 400 ml. of water, and the product was removed by vacuum filtration. In the case of the higher alcohols, the excess alcohol was removed by steam distillation, and the solid product was separated by filtration. The crude product was washed with water until the filtrates were colorless and free of chloride ion. The product after air drying was recrystallized two or more times from glacial acetic acid with the use of decolorizing carbon.

Bis[4-(2,3-dibromo)-3-nitropropoxyphenyl] Sulfone.—Compound VIIa was prepared by bromination of bis(4-allyloxy-3-nitrophenyl) sulfone (VII) in chloroform solution containing 3% by volume of glacial acetic acid. The stoppered flask was kept in the dark for 3 days at room temperature. The excess bromine was removed by addition of 10% NaOH solution and the chloroform was removed by steam distillation. The product which solidified on chilling was washed free of alkali, air-dried, and recrystallized from glacial acetic acid, m.p. 130–132°.

Bis(4-aryloxy-3-nitrophenyl) Sulfones.—The 4-phenoxy VIII and 4-*p*-toloxy IX compounds were prepared by the method of Brewster and Groenig.[4] A spontaneous reaction occurred at 120° when the bis(4-chloro-3-nitrophenyl) sulfone was added in two portions to the potassium phenolate, and the reaction was maintained at this temperature for 30 min. The reaction mixture was taken up in cold NaOH solution, and the product separated by filtration. The crude products were washed with water

TABLE I

BIS(4-ALKOXY- AND 4-ARYLOXY-3-NITROPHENYL) SULFONES



Compd.	R	Yield,[a] %	M.p., °C.[b]	Formula	—% carbon— Calcd.	Found	—% hydrogen— Calcd.	Found	—% nitrogen— Calcd.	Found
I	CH_3	79	216–217	$C_{14}H_{12}N_2O_8S$	45.65	45.76	3.28	3.20	7.60	7.49
II	C_2H_5	62	195–196	$C_{16}H_{16}N_2O_8S$	48.48	48.50	4.06	4.21	7.06	6.98
III	*n*-C_3H_7	72	197–198	$C_{18}H_{20}N_2O_8S$	50.93	50.58	4.74	4.89	6.60	6.70
IV	*n*-C_4H_9	78	160–161	$C_{20}H_{24}N_2O_8S$	53.08	53.27	5.34	5.50	6.19	6.15
V	*n*-C_5H_{11}	34	120–121	$C_{22}H_{28}N_2O_8S$	54.98	55.31	5.87	5.97	5.83	5.65
VI	*n*-$C_{12}H_{25}$[c]	17	104–105	$C_{36}H_{56}N_2O_8S$	63.87	63.99	8.33	8.45	4.13	4.24
VII	CH_2=$CHCH_2$	74	189–190	$C_{18}H_{16}N_2O_8S$	51.42	51.42	3.83	3.86	6.66	6.50
VIIa	$CH_2(Br)CH(Br)CH_2$		130–132	$C_{18}H_{16}Br_4N_2O_8S$	29.21	29.31	2.18	2.16	3.78	3.72
VIII	C_6H_5	71	173–176	$C_{24}H_{16}N_2O_8S$	58.53	58.21	3.27	3.25	5.68	5.35
IX	*p*-$CH_3C_6H_4$	74	173–175	$C_{26}H_{20}N_2O_8S$	59.99	59.44	3.87	3.96	5.38	5.67
X	*p*-$NO_2C_6H_4$	79	218	$C_{24}H_{14}N_4O_{12}S$[d]	49.48	49.60	2.42	2.45	9.62	9.76

[a] Yields calculated after one recrystallization. [b] Melting points were determined on a Fisher-Johns block and are uncorrected. [c] Reaction carried out using 140 ml. of alcohol. [d] Calcd.: S, 5.50. Found: S, 5.68.

(1) C. A. Buehler and J. E. Masters, *J. Org. Chem.*, **4**, 262 (1939).
(2) F. Ullman and J. Korselt, *Ber.*, **40**, 643 (1907).
(3) J. Annaheim. *Ann.*, **172**, 49 (1874).
(4) R. Q. Brewster and T. Groenig, "Organic Synthesis," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 445.