New Compounds

New Thio Derivatives of Carcinogenic Arylamines. IV.[1] 4-Acetamido-3-methylthiodiphenyl

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In earlier papers in this series,[1b] we described the synthesis of some new thiofluorenes related to the metabolism of the carcinogen 2-acetamidofluorene. Since we have just received word that the compound named in the title is identical with the compound isolated from a reaction of methionine and 4-acetamidodiphenyl *N*-sulfate[2] (carried out to elucidate the path of carcinogenesis of *N*-hydroxy-4-acetamidodiphenyl), we wish to report our synthesis.

Experimental Section[3]

4-Amino-3-bromodiphenyl.—To a stirred solution of 4-aminodiphenyl (1.69 g, 0.01 mol) in DMSO (8 ml) was added, dropwise, 48% HBr (1.2 ml, 0.01 mol).[4] The solution was stirred overnight at room temperature, and then heated to 95–100° for 1 hr, poured into H_2O (100 ml), and basified with NH_4OH. The brown product (1.85 g, 74%) was collected and recrystallized from EtOH, mp 64–65° (lit.[5] mp 66°).

3-Bromo-4-nitrodiphenyl.—A mixture of 4-amino-3-bromodiphenyl (2.49 g), 40% AcO_2H (35 ml), and AcOH (25 ml) was refluxed for 15 min, cooled, and then poured into H_2O (500 ml). After the light yellow emulsion was allowed to stand overnight, the yellow solid [1.6 g, a mixture of low-melting (35–40°) product and high-melting (*ca.* 140°) by-product] was collected and purified by chromatography on alumina (C_6H_6). Fractional crystallization from EtOH allowed separation of the more soluble yellow needles (1.25 g, 45%), mp 41–42° [lit.[6] bp 252–254° (7 mm)]. *Anal.* ($C_{12}H_8BrNO_2$) C, H, N.

3-Methylthio-4-nitrodiphenyl.—3-Bromo-4-nitrodiphenyl (14 g, 0.05 mol), DMSO (346 ml), and a freshly made[7] solution of $NaSCH_3$ in abs EtOH (36 ml), containing 1 equiv of the sulfide, were stirred together ($CaCl_2$ tube) for 48 hr, heated on a steam bath for 0.5 hr, then diluted with water containing a few milliliters of HCl. The yellow precipitate was filtered off, washed (H_2O), and dried giving 12.1 g (96%), mp 88–98°. Chromatography on alumina (C_6H_6) and recrystallization from EtOH gave shiny yellow plates, mp 99–100°. *Anal.* ($C_{13}H_{11}NO_2S$) C, H, N.

4-Amino-3-methylthiodiphenyl.—A mixture of 3-methylthio-4-nitrodiphenyl (4 g), 2,2′-oxydiethanol (50 ml), and 99–100% hydrazine hydrate (62 ml) was refluxed for 1.5 hr. The condenser was removed and boiling continued until the internal temperature reached 205°. Refluxing was then resumed for 2.5 hr. The mixture was cooled and diluted with H_2O. The white precipitate (3 g, 86%) was isolated and recrystallized from EtOH–H_2O to give an analytical sample, mp 55.5–56.5°. *Anal.* ($C_{13}H_{13}NS$) C, H, N.

4-Acetamido-3-methylthiodiphenyl.—4-Amino-3-methylthiodiphenyl (1 g) dissolved in C_6H_6 (5 ml) was mixed with Ac_2O (0.5 ml), boiled gently for 3 min, and evaporated to dryness to yield a white product (1.2 g, 100%). Recrystallization from EtOH gave an analytical sample, mp 120.5–121.5°. *Anal.* ($C_{15}H_{15}NOS$) C, H, N, S.

(1) (a) 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.); (b) H.-L. Pan, M. J. Namkung, and T. L. Fletcher, *J. Med. Chem.*, **11**, 1236 (1968).

(2) We thank Dr. J. A. Miller and Dr. E. C. Miller, McArdle Laboratory for Cancer Research, University of Wisconsin, for sending us this information from a paper by J. R. DeBaun, E. C. Miller, and J. A. Miller, *Cancer Res.*, in press.

(3) All melting points were taken on a Fisher-Johns block and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Analyses were performed by A. Bernhardt, Elbach über Engelskirchen, West Germany, and by Schwarzkopf Laboratories, Woodside, N. Y.

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

(5) J. R. A. Pollock and R. Stevens, Ed., "Dictionary of Organic Compounds," Vol. I, 4th ed, Oxford University Press, New York, N. Y., 1965, p 93.

(6) F. H. Case and H. A. Sloviter, *J. Amer. Chem. Soc.*, **59**, 2382 (1937).

(7) T. L. Fletcher, M. J. Namkung, and H.-L. Pan, *J. Med. Chem.*, **10**, 936 (1967); a solution containing 0.1 g of $NaSCH_3$/ml was prepared by mixing a solution (337 ml) of NaOH (20.8 g), at < 5°, in abs EtOH with 25 g of MeSH.

New Benzimidazoles

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Since a variety of pharmacological and chemotherapeutic activities have been reported[1] for benzimidazole derivatives, a number of previously unreported compounds containing the benzimidazole nucleus were prepared for biological screening. The substances and associated data are listed in Tables I and II. The methods of preparation are adaptations of known procedures.

Experimental Section[2]

Method A.—Equimolar amounts of the appropriate 2-methylbenzimidazole and aromatic aldehyde[3] were dissolved in Ac_2O and the solution refluxed for 24 hr during 3 working days. The Ac_2O was decomposed with ice–H_2O and the solution neutralized with NH_4OH. In the case of **2**, the acetoxy intermediate could not be isolated in a pure state so it was saponified with NaOH to the free phenol which was purified as the hydrochloride. Compound **3** was prepared by NaOH hydrolysis of **5** and **4** was obtained by heating **7** with pyridine·HCl; yields are based on the starting materials **5** and **7**.

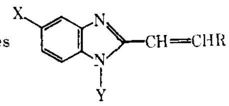
Method B.—Equimolar amounts (usually about 0.03 mol or approximately 5 g) of the appropriate 2-methylbenzimidazole and aromatic aldehyde were mixed in a large test tube and heated in a wax bath at 200° for 2 hr during which the H_2O which formed distilled out of the reaction mixture. The residual mass

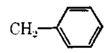
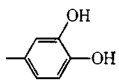
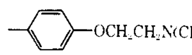
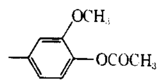
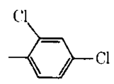
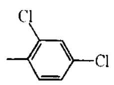
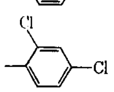
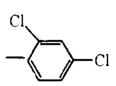
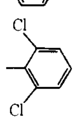
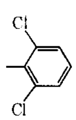
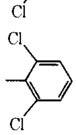
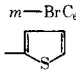
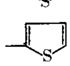
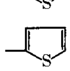
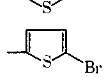
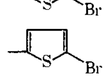
(1) Illustrative examples include (a) cholesterol-lowering: M. L. Black, G. Rodney, and D. B. Capps, *Biochem. Pharmacol.*, **17**, 1803 (1968); (b) analgetic: A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, *Experientia*, **13**, 400 (1957); (c) antifungal: S. Herrling, H. Sous, W. Krüpe, G. Osterloh, and H. Mückter, *Arzneim.-Forsch.*, **9**, 489 (1959); (d) antiviral: I. Tamm, H. J. Eggers, R. Bablanian, A. F. Wagner, and K. Folkers, *Nature*, **223**, 785 (1969); (e) anthelmintic: H. D. Brown, A. R. Matzuk, I. R. Ilves, L. H. Peterson, S. A. Harris, L. H. Sarett, J. R. Egerton, J. J. Yakstis, W. C. Campbell, and A. C. Cuckler, *J. Amer. Chem. Soc.*, **83**, 1764 (1961).

(2) Melting points are corrected. With the exceptions noted in the tables, analytical results were within ±0.4% of the theoretical values.

(3) Except for 4-(2-dimethylaminoethoxy)benzaldehyde, which was prepared by the procedure of M. W. Goldberg, and S. Teitel, U. S. Patent 2,879,293 (1959), the starting aldehydes were obtained from commercial sources.

Table I

2-Vinylbenzimidazoles 

	R	X	Y	Method	Recrystn solvent	Mp, °C	Yield, %	Formula	Analyses
1	C_6H_5	H			EtOH	179–180	75	$C_{22}H_{18}N_2$	N
2	*m*-HOC_6H_4	H	H	A	H_2O(HCl)	286–288 dec[a]	45	$C_{15}H_{12}N_2O \cdot HCl$	C, H, N
3	*p*-HOC_6H_4	H	H	A	EtOH	310–312 dec	93	$C_{15}H_{12}N_2O \cdot HCl$	C, H, Cl[b]
4		H	H	A	H_2O	275–276 dec	87	$C_{15}H_{12}N_2O_2 \cdot HCl$	C, H, Cl[c]
5	*p*-$C_6H_4OCOCH_3$	H	H	A	EtOH	231–232	30	$C_{17}H_{14}N_2O_2$	N
6		H	H	A	EtOH	183.5–184.5	11	$C_{19}H_{21}N_3O$	C, H
7		H	H	A	DMF–H_2O	237–238	34	$C_{18}H_{16}N_2O_3$	C, H
8[d]		H	H	A	EtOH	258.5–260	82	$C_{15}H_{10}Cl_2N_2$	N
9[e]		H	CH_3		EtOH	168–169	84	$C_{16}H_{12}Cl_2N_2$	C, H
10		NO_2	H	A	AmOH	281–282	55	$C_{15}H_9Cl_2N_3O_2$	N
11		Cl	H	B	Xylene	145–149	71	$C_{15}H_9Cl_3N_2$	Cl
12		H	H	B	EtOH	219–220	52	$C_{15}H_{10}Cl_2N_2$	N, Cl
13		NO_2	H	B	$MeOCH_2CH_2OH$	261–262	65	$C_{15}H_9Cl_2N_3O_2$	Cl
14		Cl	H	B	EtOH–H_2O	219.5–220.5 dec	71	$C_{15}H_9Cl_3N_2$	Cl
15	*m*-BrC_6H_4	H	H	B	$MeOCH_2CH_2OH$	232–233	80	$C_{15}H_{11}BrN_2$	C, H, N, Br
16		H	H	B	EtOH	242–243 dec[f]	44	$C_{13}H_{10}N_2S$	C, H, N
17		NO_2	H	B	$MeOCH_2CH_2OH$	287–291 dec	50	$C_{13}H_9N_3O_2S \cdot HCl$	Cl, N, S[g]
18		Cl	H	B	Toluene	201.5–202.5	54	$C_{13}H_9ClN_2S$	S, Cl
19[h]		H	H		EtOH	245.5–247.5 dec	70	$C_{13}H_9BrN_2S \cdot HBr$	S
20[i]		Cl	H		$MeOCH_2CH_2OH$	298–299 dec	58	$C_{13}H_8BrClN_2S \cdot HBr$	S

[a] HCl salt. Base mp 193–194° from xylene (C, H, N). [b] HCl salt. H: calcd, 4.80; found, 5.40, 5.35. Cl: calcd, 13.00; found 13.49, 13.58. [c] HCl salt. H: calcd, 4.54; found, 5.13, 5.40. [d] Previously prepared by Dr. W. Wenner. [e] Methiodide mp 287–288° dec (C, H, N, I). [f] Mp 234–235° was reported by Kalle A.-G., German Patent 1,105,713; *Chem. Abstr.*, **56,** 8215 (1962). [g] Cl: calcd, 11.52; found, 10.85. [h] HBr salt. Base mp 185–187.5° from EtOH–H_2O (Br, N, S). [i] HBr salt.

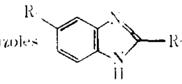
was then extracted 3 times with 200-ml portions of boiling H_2O, at which time it usually solidified, to remove unreacted starting materials. The residue was then crystallized from an organic solvent.

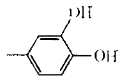
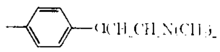
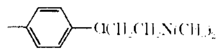
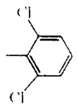
N-Alkylation (1 and 9).—2-Styrylbenzimidazole[4] and 10% *M* excesses of KOH and $PhCH_2Cl$ were dissolved in EtOH and the solution refluxed for 2.5 hr. The precipitated KCl was filtered and the filtrate diluted with H_2O, and cooled, during which process 1 separated. Compound **9** was prepared from **8** by refluxing 1 hr with excess MeI in EtOH in the presence of NaOH; the product separated from the hot reaction mixture. Quaternization of **9** was accomplished by refluxing in Me_2CO with an excess of MeI; the product separated as the reaction progressed.

Bromination (19 and 20).—The Br-free precursors (**16, 18**) were dissolved in glacial HOAc and an equimolar solution of

(4) R. Weidenhagen, *Ber.*, **69**, 2263 (1936).

Table II

Additional Benzimidazoles 

	R²	R³	Method	Recrystn solvent	Mp, °C	Yield, %	Formula	Analyses
21		H		H_2O	253–254[a]	84	$C_{13}H_{10}N_2O_2 \cdot HCl$	N, Cl
22		H	C	50% EtOH	184–185[b]	31	$C_{17}H_{19}N_3O \cdot 2C_4H_6O_6$	C, H, N
23		NO_2	C	EtOH	212–214	57	$C_{17}H_{18}N_4O_3$	C, H
24		Cl	C	EtOH	240.5–241.5	56	$C_{13}H_7Cl_3N_2$	Cl
25		Cl	C	Xylene	226.5–227.5	28	$C_{11}H_7ClN_2S$	Cl, S

[a] HCl salt: Cl calcd, 13.49; found 12.86. [b] Tartaric acid salt.

Br_2 in CCl_4 was added slowly with stirring at room temperature. The hydrobromide of the brominated product separated from the reaction mixture. The location of the Br substituent was verified by nmr spectroscopy.

Method C.—Equimolar amounts of the *o*-phenylenediamine and aromatic aldehyde were heated in $PhNO_2$ in a distillation apparatus until the distillate came over clear (H_2O no longer forming, usually about 30 min). The residual distilland was cooled, and the product was collected and recrystallized.

Compound 21 was prepared by refluxing a solution of 4-(2-benzimidazolyl)guaiacol[4] in pyridine·HCl for 45 min, then pouring over ice and collecting the product. It was recrystallized from H_2O containing small amounts of $NaHSO_3$ and HCl.

Acknowledgments.—The author thanks Drs. A. Steyermark and F. Scheidl for microanalyses, Mr. S. Traiman for ir spectra and Dr. T. Williams for nmr spectra and interpretation.

Antitumor Activities of Some Schiff Bases

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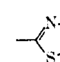
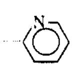
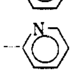
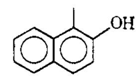
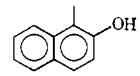
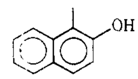
Schiff bases are known to slow the growth of some animal tumors.[1] More compounds of this type have now been prepared and have been screened by the Cancer Chemotherapy National Service Center. None of these compounds showed activity against lymphoid leukemia L1210 in the mouse, but some slowed the growth of intramuscular Walker sarcoma in the rat[2] as shown in Table I.

(1) E. M. Hodnett and W. Willie, *Proc. Okla. Acad. Sci.*, **46**, 107 (1966).
(2) "Protocols for Screening Chemical Agents and Natural Products against Animal Tumors and Other Biological Systems," Cancer Chemotherapy National Service Center (CCNSC), *Cancer Chemother. Rept.*, **25**, 1 (1962), and as modified (Jan 1966).

Table I

Schiff Bases Prepared

$R^1CH{=}NR^2$

R¹	R²	Intramuscular Walker sarcoma of the rat[a]: Dose, mg/kg	T/C[b]	Ref
C_6H_4-2-OH		400	0.83	c
	C_6H_4-4-OH	400	1.03	d
	C_6H_3-2-OH-5-NO_2	400	0.94	e
	C_6H_5	400	0.89	f
	C_6H_4-2-OH	400	0.78	f
	C_6H_4-4-OH	400	0.58	f

[a] The screening data were supplied through the kindness of Dr. Harry B. Wood, Jr., of the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda, Md. Assays were performed according to CCNSC specifications as reported in ref 2. [b] Effectiveness against intramuscular Walker sarcoma of the rat is measured by weights of tumors of treated rats (T) compared to the tumors of control rats (C); the value of T/C must be 0.53 or less for significant activity. [c] Mp 77–78°. *Anal.* ($C_{10}H_8N_2OS$) C, H, N. [d] G. N. Walker and M. A. Klett, *J. Med. Chem.*, **9**, 624 (1966). [e] Mp 195–196°. *Anal.* ($C_{12}H_9N_3O_3$) C, H, N. [f] I. A. Savich, V. V. Zelentsov, and I. Spitsynn, *Vestnik Moskov Univ. Ser. Mat. Mekh., Astron., Fiz., Khim.*, **11**, 233 (1956); *Chem. Abst.*, **53**, 1264*h* (1959).

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