heated very cautiously in an atmosphere of nitrogen, the yellow crystals sublime and reform in a cooler portion of the tube. Upon stronger heating, some disproportionation occurs and white crystals of chromium hexacarbonyl are observed further along the tube. Finally, complete decomposition results in the deposition of a metallic mirror of cadmium and chromium.

Acknowledgment.—We are indebted to Dr. Francis J. Norton, of the Research Laboratory of the General Electric Company, for preparing and interpreting mass spectra of our samples of chromium carbonyl, chromium carbonyl hydride, and products produced by spontaneous decomposition of the hydride upon standing at room temperatures.

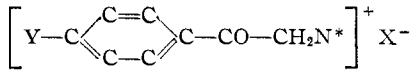
DEPARTMENT OF CHEMISTRY
YALE UNIVERSITY
NEW HAVEN, CONNECTICUT RECEIVED JUNE 8, 1951

Preparation of Some Sulfonium Salts as Possible Anticancer Agents

BY HENRY A. RUTTER, JR.[1]

The preparation of sulfonium halides as possible anticancer agents was prompted by the structural similarity between quadrivalent sulfonium compounds and quaternary ammonium derivatives.

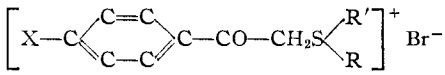
Hartwell and Kornberg[2] prepared several aralkyl quaternary ammonium halides of the type I which had anticancer activity.



I

The nitrogen was contained in a heterocyclic ring such as pyridine or α-picoline.

In the present investigation a series of aralkyl sulfonium bromides of the type II were prepared by reaction of the appropriate phenacyl bromide with dialkyl sulfides according to the method of Bost and Schultze[3] for the preparation of *p*-phenylphenacyl sulfonium bromides.



II

where X is H, CH_3, C_6H_5, Br, Cl and CH_3O and R and R′ are alkyl groups. In addition one meta-nitro derivative has been prepared.

These compounds are listed in Table I.

A preliminary report indicates that six of the phenacyl sulfonium bromides are somewhat effective as tumor necrotizing agents at dosages of 150 to 250 mg. per kilogram of body weight against Sarcoma 37 in mice.[4]

Grateful acknowledgment is made to Dr. M. X. Sullivan for his advice and encouragement during this investigation.

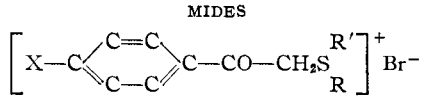
(1) Taken from thesis submitted by Henry A. Rutter, Jr., in partial fulfillment of the requirements for the degree of Ph.D. at The Division of Chemistry, Graduate School, Georgetown University, Washington, D. C.

(2) J. L. Hartwell and S. R. L. Kornberg, THIS JOURNAL, **68**, 868 (1946).

(3) R. W. Bost and H. C. Schultze, *ibid.*, **64**, 1165 (1942).

TABLE I

PHENACYL AND SUBSTITUTED PHENACYL SULFONIUM BROMIDES



X	R	R′	Formula	Yield, %	M.p., °C. (uncor.)	Bromide ion, %[a] Calcd.	Found
H	C_3H_7	C_3H_7	$C_{14}H_{21}OSBr$	13	93–94	25.23	25.20
H	C_4H_9	C_4H_9	$C_{16}H_{25}OSBr$	23	88–89	23.18	22.90
H	C_4H_9	C_2H_5	$C_{14}H_{21}OSBr$	63	103–104	25.23	25.05
CH_3	CH_3	CH_3	$C_{11}H_{15}OSBr$	51	112	29.04	28.71
CH_3	C_3H_7	C_3H_7	$C_{15}H_{23}OSBr$	12	98–99	24.12	24.41
CH_3	C_4H_9	C_4H_9	$C_{17}H_{27}OSBr$	28	99–100	22.24	21.99
CH_3	C_4H_9	C_2H_5	$C_{15}H_{23}OSBr$	12	97	24.12	23.74
C_6H_5	C_2H_5	C_2H_5	$C_{18}H_{21}OSBr$	31	123–124	21.9	21.47
C_6H_5	C_3H_7	C_3H_7	$C_{20}H_{25}OSBr$	25	113–114	20.37	20.10
C_6H_5	C_4H_9	C_2H_5	$C_{20}H_{25}OSBr$	14	96–97	20.37	20.21
Br	CH_3	CH_3	$C_{10}H_{12}OSBr_2$	53	127	23.52	23.31
Br	C_2H_5	C_2H_5	$C_{12}H_{16}OSBr_2$	53	119–120	21.73	21.40
Br	C_3H_7	C_3H_7	$C_{14}H_{20}OSBr_2$	49	107–108	20.20	19.9
Cl	CH_3	CH_3	$C_{10}H_{12}OSBrCl$	27	128–129	27.03	27.14
Cl	C_3H_7	C_3H_7	$C_{14}H_{20}OSBrCl$	29	111	22.72	22.85
Cl	C_4H_9	C_4H_9	$C_{16}H_{24}OSBrCl$	21	99	21.04	20.88
Cl	C_4H_9	C_2H_5	$C_{14}H_{20}OSBrCl$	34	102–103	22.72	22.48
CH_3O	C_2H_5	C_2H_5	$C_{13}H_{19}O_2SBr$	13	106–107	25.03	24.71
CH_3O	C_3H_7	C_3H_7	$C_{15}H_{23}O_2SBr$	15	100	23.01	22.62
m-NO_2	C_3H_7	C_3H_7	$C_{14}H_{20}NO_2SBr$	6	97–98	22.06	21.71

[a] Mohr analysis, average of two.

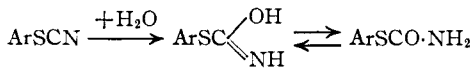
(4) Acknowledgment is made to Dr. Jonathan L. Hartwell, National Cancer Institute, for the report on the tumor necrotizing activity of the compounds. The final report dealing with the biological activity of these compounds will be made later.

CHEMO-MEDICAL RESEARCH INSTITUTE
GEORGETOWN UNIVERSITY
WASHINGTON, D. C. RECEIVED JUNE 25, 1951

Thiocarbamates. III.[1] Aryl Thiocarbamates from Aryl Thiocyanates

BY R. RIEMSCHNEIDER, F. WOJAHN AND G. ORLICK[2]

As reported elsewhere,[1,3] the action of concentrated sulfuric acid followed by treatment with ice-water serves, in most cases, to transform aryl thiocyanates into the corresponding thiocarbamates



The reaction is of preparative as well as of analytical value. We have found that the reaction is superior to older procedures for the preparation of thiocarbamates[4] with respect to general applicability,

(1) R. Riemschneider, Paper I, *Mitt. physiol. chem. Inst.*, R 30. Feb., 1949; Paper II, *Chimica e industria (Milan)*, **33**, 483 (1951) (presented Sept. 19, 1950, before the VI National Congress of Pure and Applied Chemistry, Milan).

(2) Address of the authors: Hohenzollernplatz 1, Berlin-Nikolassee,

(3) *Pharmazie*, **4**, 460 (1949); *Chim. et Ind.*, **64**, Sonderheft, Sept., 99 (1950); *Pharm. Zentralhalle*, **89**, 108 (1950); further references may be found in Paper I of this series.[1]

(4) H. L. Wheeler and B. Barnes, *Am. Chem. J.*, **22**, 141 (1899); A. Fleischer, *Ber.*, **9**, 988 (1876); N. A. Langlet, *ibid.*, **24**, 3848 (1891); B. Hohnberg, *ibid.*, **47**, 159 (1914); A. Knorr, *ibid.*, **49**, 1735 (1916); E. Biillmann and J. Bjerrum, *ibid.*, **50**, 503 (1917); M. H. Rivier, *Bull. soc. chim.*, [4] **1**, 733 (1907); R. Conrad and F. Salomon, *J. prakt.*

TABLE I

Substituted phenyl thiocyanates: Derivative	B.p. or m.p.,[b] °C.	Derived aryl-thiocarbamates from aryl thiocyanates: Yield,[c] %	Solvents[d]	M.p., °C.	Crystal form	Formula	N analyses, %: Calcd.	Found	Precipitate produced by alc. silver nitrate
Unsubstituted	71–73(1.5)[a]	87	B	98[e]	Needles	C_7H_7NOS	9.15	9.14	Gelatinous
2-Methyl	122.5(15.5)[a]	88	B	139	Tetrahedra	C_8H_9NOS	8.38	8.75	Cheesy
3-Methyl[f]	110–114(10)[a]	89	B	108.5	Rods	C_8H_9NOS	8.38	8.45	Yellow, flocculent
4-Methyl	116–118(10)[a]	89	B	175 dec.	Rods, plates	C_8H_9NOS	8.38	8.40	Yellow-green, gelatinous
2-Chloro	[g]	88	T	145	Needles	C_7H_6NOSCl	[m]		Gelatinous
3-Chloro	[g]	87	T	145.5	Rosettes	C_7H_6NOSCl	[n]		Bright yellow, gelatinous
4-Chloro	36	95	B	176 dec.	Plates	C_7H_6NOSCl	[o]		Gelatinous
4-Bromo	55	100	BT	184 dec.	Plates	C_7H_6NOSBr	6.04	6.10	Gelatinous
4-Iodo	50.0–50.5	94	T	187 dec.	Scales	C_7H_6NOSJ	[p]		Flocculent
4-Cyano	127–128	85	T	165 dec.	Lances	$C_8H_6N_2OS$[l]	[q]		Flocculent, finely divided
3-Nitro	49–51	98	T	124	Yellow needles	$C_7H_6N_2O_3S$	[r]		Bright yellow, flocculent
4-Nitro	128–129	100	T	157 dec.	Needles	$C_7H_6N_2O_3S$	14.14	14.13	Yellow, flocculent
4-Hydroxy	56.0–57.5	45	DB	172.5		$C_7H_7NO_2S$	8.28	8.15	Yellow, flocculent
4-Methoxy	33–34	59	BT	131	Needles	$C_8H_9NO_2S$	7.65	8.06	Yellow-green, gelatinous
4-Ethoxy	46–47	73	B	127	Scales	$C_8H_{11}NO_2S$	7.10	7.35	Bright yellow, gelatinous
3-Carboxy[f]	178 dec.	87	Ph[h]	184 dec.	Microcrystalline	$C_8H_7NO_3S$	7.10	7.03	Flocculent
4-Carboxy[f]	195 dec.	77	Ph[h]	300[i]	Not recognizable	$C_8H_7NO_3S$	7.10	6.71	Bright yellow, flocculent
4-Amino	57.0–57.5	67[j]	BT	131	Needles	$C_7H_8N_2OS$	[s]		Bright yellow, flocculent
4-N-Methylamino	43.0–43.5	73[j]	BT	135	Needles	$C_8H_{10}N_2OS$	[t]		Yellow, flocculent
4-N,N-Dimethylamino	73–74	86[j]	B	131.5	Needles	$C_9H_{12}N_2OS$	14.28	14.10	Orange, flocculent
4-N-Ethylamino	55–56	80[j]	B	144	Needles	$C_9H_{12}N_2OS$	[u]		Yellow, flocculent
4-N,N-Diethylamino	138(1)[a]	87[j]	BP	108.5	Needles	$C_{11}H_{16}N_2OS$	12.49	12.89	Bright yellow, flocculent
3-Methyl-4-amino	68	72[j]	BT	136.5	Plates	$C_8H_{10}N_2OS$	15.37	15.41	Flocculent
2-Chloro-4-amino	75	82[j]	T	145.5	Plates	$C_7H_7N_2OSCl$	13.82	13.95	Bright yellow, flocculent
3-Chloro-4-amino[f]	61	77[j]	BT	159.5	Plates, needles	$C_7H_7N_2OSCl$	13.82	14.13	Bright yellow, flocculent
3-Nitro-4-amino	113–114	93	BN	176 dec.	Red rods, needles	$C_7H_7N_3O_3S$	19.71	19.66	Cherry-red, flocculent
3-Methoxy-4-amino	64	54[j]	T	136		$C_8H_{10}N_2O_2S$	14.13	14.00	Yellow-green, flocculent
4-Thiocyano	107–108	93[j]	[k]	199 dec.	Powdery	$C_8H_8N_2O_2S_2$	12.27	12.21	Bright yellow, cheesy
Appendix									
1-Naphthyl thiocyanate	53	94	BT	135.5	Needles	$C_{11}H_9NOS$	[v]		Gelatinous
1-(4-Aminonaphthyl) thiocyanate	146–147	72	T	165	Crystalline	$C_{11}H_{10}N_2OS$	12.84	12.80	Yellow, flocculent

[a] Boiling point (mm.). [b] Melting points are uncorrected. [c] Yields of crude, dried products are given. [d] B, benzene, T, toluene, D, dioxane, Ph, phenetole, P, petroleum ether, N, nitrobenzene. [e] A. Knorr, *Ber.*, **49**, 1735 (1916), prepared this compound from phenyl thiocyanate by the action of dry hydrogen chloride in ethanol; mixed m.p. of the present preparation with a sample obtained according to Knorr's method: 97°. [f] These thiocyanates are not recorded in the literature through *C.A.*, **44**, 22 (1950). [g] Purified by steam distillation. [h] The solutions were not heated beyond 120°. [i] Sinters at 275° and is completely decomposed at 308°. [j] Isolated by neutralization of the sulfuric acid–ice-water mixture with sodium bicarbonate. [k] Obtained by extraction of the crude product with hot dioxane. [l] Characterized as a cyanothiocarbamate by its behavior toward alcoholic alkali (*cf. Pharmazie*, **4**, 462 (1949)). [m] Calcd. C, 44.81; H, 3.22. Found: C, 45.14; H, 3.15. [n] Calcd. S, 17.09. Found: S, 17.03. [o] Calcd. C, 44.81; H, 3.22. Found: C, 44.83; H, 3.25. [p] Calcd. S, 11.49. Found; S, 11.85. [q] Calcd. S, 17.98. Found: S, 17.97. [r] Calcd. C, 42.42; H, 3.05. Found: C, 42.39; H, 3.29; [s] Calcd. S, 19.06. Found: S, 19.38. [t] Calcd. S, 17.59. Found: S, 17.99. [u] Calcd. S, 16.33. Found: S, 16.24. [v] Calcd. S, 15.77. Found: S, 15.98.

yields obtained, and simplicity of operation. The reaction proved to be unsatisfactory in the cases of several *o*-substituted phenyl thiocyanates, *e.g.*, the *o*-carboxyl-, *o*-methoxy- and *o*-nitro-derivatives; aryl thiocyanates sensitive to concentrated sulfuric acid, *e.g.*, thiocyanophenols, also gave unfavorable results. Thus, the corresponding thiocarbamates are, in these cases, best prepared by one of the older procedures.[4]

Thirty aryl thiocarbamates have been prepared by the sulfuric acid method; descriptive and analytical data for these compounds are listed in the table I. The compounds give precipitates with alcoholic silver nitrate.

Experimental

The aryl thiocyanate (2 g.) is treated slowly with shaking, and with ice cooling, with 10 cc. of 95% sulfuric acid. The mixture is allowed to stand at 0° to 5° for 15 hours, and is poured on ice. The precipitate is collected, washed with water, and dried in air, or, in some cases, in vacuum with slight warming. If a high-boiling solvent, *e.g.* phenetole, is used for recrystallization, the solution should be heated for as brief a period as possible in order to avoid decomposition of the solutes. The procedure given has been applied to quantities up to 10 g. of aryl thiocyanate, with correspondingly increased volumes of sulfuric acid.

Chem., [2] **10**, 28 (1874); M. Battegay and R. Krebs, *Compt. rend.*, **206**, 919 (1938); Badische Anilin und Soda Fabrik, A. G., German Patent 175,070; *Chem. Zentr.*, **77**, 1466 (1906).

CHEMICAL INSTITUTE OF THE FREE UNIVERSITY
BERLIN, GERMANY RECEIVED APRIL 9, 1951

New Benzimidazoles from Polyhydroxy Acids[1]

BY DAVID A. ROSENFELD, JAMES W. PRATT, NELSON K. RICHTMYER AND C. S. HUDSON

Incidental to other researches now in progress we have prepared several benzimidazoles whose descriptions may well be presented together at this time. The first of these is derived from the condensation of *o*-phenylenediamine with D-glyceric acid. Although the benzimidazole from the simplest hydroxy acid, glycolic acid, has long been known,[2] and that of the 3-desoxyglyceric, *i.e.*, lactic acid even longer,[3] a benzimidazole of a glyceric acid has not been reported previously.

In one of Griess and Harrow's classic papers[4] on the action of aromatic diamines on sugars they included the reaction between D-glucose and 3,4-diaminotoluene acetate. The product crystallized as "small white warts" and from its composition is presumed to be identical[1] with the benzimidazole that we have now obtained by the condensation of D-gluconic acid with 3,4-diaminotoluene in the presence of concentrated hydrochloric acid by the procedure of Moore and Link.[5] The melting point and specific rotation are here recorded for the first time.

Benzimidazoles derived from "L-α-rhamnohexonic" and "D-β-galaheptonic" acids are also described. The rotations of these four new benzimidazoles are in accord with the "benzimidazole rule," which states[6]: "Whenever the hydroxyl group on the second (or alpha) carbon atom of an aldonic acid is on the right in the conventional projection formula of Fischer, the rotation of the derived benzimidazole is positive and, conversely, when the hydroxyl group is on the left, the rotation of the benzimidazole is negative."

Lohmar, Dimler, Moore and Link[7] have prepared the dibenzimidazoles and the respective dihydrochlorides from galactaric (= mucic), D-glucaric (= D-saccharic) and D-mannaric (= D-mannosaccharic) acids. We have now extended this list, for purposes of characterization and identification, by adding data for the corresponding derivatives of L-threaric acid (= L(+)-tartaric acid, the ordinary dextrorotatory tartaric acid commonly present in grapes).

Experimental

2-(D-*glycero*-1,2-Dihydroxyethyl)-benzimidazole.—Two grams of calcium D-glycerate dihydrate, prepared from methyl α-D-mannopyranoside by periodate oxidation followed by bromine oxidation and subsequent hydrolysis as described by Jackson and Hudson,[8] was refluxed for 3 hours with 1.6 g. of *o*-phenylenediamine in 40 ml. of 4 *N* hydrochloric acid by heating in an oil-bath kept at 130 ± 5°. Because no crystallization occurred when the solution was made ammoniacal and concentrated, the product was isolated through its copper salt by the procedure of Moore and Link.[5] The benzimidazole thus obtained weighed 0.70 g. (28%). It was recrystallized from a mixture of 30 parts of water and 5 parts of ethanol, forming slightly tan-colored needles with m.p. 184–186° (dec.) and $[\alpha]^{20}D$ +39.6° in *N* hydrochloric acid (*c* 3.6).

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.78; H, 5.67; N, 15.54.

5-Methyl-2-(D-*gluco*-1,2,3,4,5-pentahydroxypentyl)-benzimidazole.—Calcium D-gluconate and 3,4-diaminotoluene dihydrochloride were condensed in the presence of a small excess of hydrochloric acid according to the general procedure of Moore and Link.[5] The product, obtained in 70% yield, was recrystallized thrice from 15 parts of water as clusters of tiny needles which united to form larger masses of "warts," as Griess and Harrow[4] had described them earlier. The benzimidazole melted at 212–214° (dec.) and showed $[\alpha]^{20}D$ +9.2° in *N* hydrochloric acid (*c* 2).

Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.93. Found: C, 55.20; H, 6.44; N, 9.67.

2-(L-*manno*-L-*gala*-*hepto*-1,2,3,4,5-Pentahydroxyhexyl)-benzimidazole.—Crystalline "L-α-rhamnohexonic lactone" (=7-desoxy-L-manno-L-*gala*-heptonic lactone) was prepared by a modification of the method of Fischer and Tafel[9] for the addition of hydrogen cyanide to L-rhamnose. A mixture of 5.6 g. of the lactone and 3.3 g. of *o*-phenylenediamine was condensed in the presence of hydrochloric acid as catalyst according to the procedure of Moore and Link.[5] The isolated benzimidazole weighed 4.5 g. (54%) and was purified by 3 recrystallizations, as needles, from 70 parts of 50% ethanol. It then melted at 266–268° (dec.) and had the rotation $[\alpha]^{20}D$ −41.5° in *N* hydrochloric acid (*c* 2.5).

Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.93. Found: C, 55.37; H, 6.34; N, 9.88.

The same benzimidazole was obtained in 70% yield by the condensation of 2.7 g. (0.009 mole) of 7-desoxy-L-manno-L-*gala*-heptonic phenylhydrazide[10] with 1.1 g. (0.01 mole) of *o*-phenylenediamine in a similar manner. The

(1) For a review of the 2-(*aldo*-polyhydroxyalkyl)-benzimidazoles see N. K. Richtmyer, *Advances in Carbohydrate Chem.*, **6**, 175 (1951).

(2) A. Bistrzycki and G. Przeworski, *Ber.*, **45**, 3483 (1912).

(3) M. Georgescu, *ibid.*, **25**, 952 (1892); see R. J. Dimler and K. P. Link, *J. Biol. Chem.*, **143**, 557 (1942), for those of the optically active forms.

(4) P. Griess and G. Harrow, *Ber.*, **20**, 2205 (1887).

(5) S. Moore and K. P. Link, *J. Biol. Chem.*, **133**, 293 (1940).

(6) N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **64**, 1612 (1942).

(7) R. Lohmar, R. J. Dimler, S. Moore and K. P. Link, *J. Biol. Chem.*, **143**, 551 (1942).

(8) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **59**, 994 (1937).

(9) E. Fischer and J. Tafel, *Ber.*, **21**, 1657 (1888); see also E. L. Jackson and C. S. Hudson, THIS JOURNAL, **56**, 2455 (1934).

(10) E. Fischer and F. Passmore, *Ber.*, **22**, 2728 (1889).