NOTES

Synthesis of Potential Anticancer Agents. VIII. Benzaldehyde Mustard Derivatives and Related Compounds[1,2]

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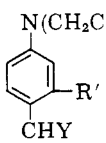
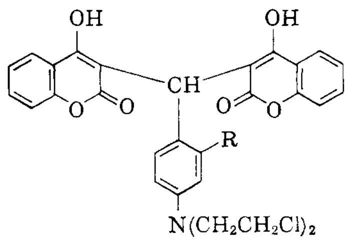
Since several potential anticancer agents derived from 4-[N,N-bis-(2-chloroethyl)amino]benzaldehyde (benzaldehyde mustard) and from 4[bis(2-chloroethyl)amino]-*o*-tolualdehyde exhibited wide orders of anticancer activity,[3-6] we have investigated other derivatives of these aldehydes. Most of these are summarized in Table I.

The previously reported hydrazide I (R = $-CH_2CN$, R′ = H)[5] had some activity and hence several other hydrazides of the type I have been prepared. These were at best only slightly active against the Dunning leukemia in rats when administered in doses of up to 500 mg./kg. to an established tumor on day seven.[7]

In view of the activity of several of our Schiff bases (II),[4,6] hydrazones (III) were prepared in order to determine the effect on activity of an additional nitrogen. These hydrazones, as contrasted with the activity of the Schiff bases, ranged from inactive to slightly active when tested as mentioned above.[7] The most active (III, R = *p*-FC_6H_4-, R′ = H) was much less active than the corresponding Schiff base (II, R = *p*-FC_6H_4-, R′ = CH_3). Wiley and Irick[8] have also prepared some related hydrazones.



I, Y==NNHCOR
II, Y==NR
III, Y==NNHR



IV

(1) Part VII, F. D. Popp, E. Cullen, R. B. Davis and W. Kirsch, *J. Med. Pharm. Chem.*, **5**, 398 (1962).

(2) This work was supported in part by research grants from the American Cancer Society (T 177A) and from the National Cancer Institute, U. S. Public Health Service (CY 4814C1).

(3) F. D. Popp, *J. Chem. Soc.*, 5271 (1960).

(4) F. D. Popp, *J. Org. Chem.*, **26**, 1566 (1961).

(5) F. D. Popp, *ibid.*, **26**, 3019 (1961).

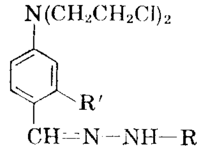
(6) F. D. Popp and W. Kirsch, *idid.*, **26**, 3858 (1961).

(7) Drs. Ralph Jones, Jr., and Leo Rane, private communication.

(8) R. H. Wiley and G. Irick, *J. Org. Chem.*, **26**, 593 (1961).

TABLE I

ALDEHYDE DERIVATIVES



R	R′	M.p., °C.[a]	Yield, %	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
—$CSNH_2$	H	160[b,c]	97	45.14	5.05	17.55	45.29	5.04	17.60[d]
—$CSNH_2$	CH_3	203[b,c]	90	46.85	5.44		46.67	5.44[e]	
—COC_6H_5	H	186–187	99	59.35	5.26	11.54	59.23	5.27	11.69
—COcyclopropyl	H	182–184	94	54.88	5.83	12.80	54.80	5.86	12.88
—COcyclopropyl	CH_3	201–203	76	56.14	6.19	12.28	56.24	6.21	12.14
—COC_6H_4OH-*o*	H	206–207	83	56.85	5.04	11.05	56.82	5.09	11.02
—C_6H_4F-*p*	H	116–118	61	57.63	5.12	11.86	57.69	5.25	11.99
—C_6H_4Br-*p*	H	165–166[f]	88	49.18	4.37	10.12	49.43	4.50	9.97
—$C_6H_4CO_2H$-*p*	H	221–223	91	56.85	5.04	11.05	56.86	5.18	11.48
—$SO_2C_6H_4CH_3$-*p*	H	178–179	99	52.17	5.11	10.14	51.94	5.13	9.87
—3-quinolyl·HCl	H	214–218	46	56.68	5.00	13.22	56.35	5.45	13.10
—2-benzothiazolyl	H	187–189	93	54.96	4.61	14.24	54.98	4.55	14.36
—2-benzothiazolyl	CH_3	211–212	80	56.02	4.95	13.75	56.12	5.08	13.75
—C_6H_5, —CH_3[g]	H	105–107	96	61.71	6.04	12.00	61.59	6.07	11.92

[a] Recrystallized from absolute ethanol unless otherwise stated. [b] When placed in melting point apparatus slightly below m.p. [c] Analytically pure without recrystallization. [d] Calcd.: Cl, 22.21. Found: Cl, 22.25. [e] Calcd.: Cl, 21.28. Found: Cl, 21.50. [f] Recrystallized from absolute ethanol–ethyl acetate. [g] Prepared from 1-methyl-1-phenylhydrazine.

In view of the antituberculous activity of some thiosemicarbazones[9] it was decided to prepare this type of derivative of the mustard aldehydes. The thiosemicarbazones prepared, as well as their crude copper complexes, were completely inactive in a variety of tumor systems.

The condensation of the mustard aldehydes with 4-hydroxycoumarin[10] gave a good yield of the dicumarol analogs IV.

Experimental[11]

Thiosemicarbazones.—A hot solution of 0.91 g. (0.01 mole) of thiosemicarbazide in 30 ml. of water and 2 ml. of glacial acetic acid was added to 0.01 mole of the aldehyde in 25 ml. of ethanol and the mixture was heated for 15 min. Cooling and filtration gave the thiosemicarbazones described in Table I. The copper complexes of these derivatives were prepared by a standard method[12] but were not purified.

Other Aldehyde Derivatives.—A hot solution of 0.01 mole of the aldehyde in a minimum of absolute ethanol was added to a hot solution of 0.01 mole of the hydrazide, hydrazine, or hydrazine salt in a minimum of absolute ethanol[13] and the mixture was refluxed for 15 min. Cooling and filtration gave the compounds listed in Table I.

Dicumarols.—A mixture of 0.015 mole of benzaldehyde mustard and 0.02 mole of 4-hydroxycoumarin in absolute ethanol was refluxed for 15 min. Cooling and filtration gave 5.13 g. (93%) of solid, m.p. 230–231.5°, insoluble in hot ethanol.

Anal. Calcd. for $C_{29}H_{23}Cl_2NO_6$: C, 63.05; H, 4.20; N, 2.72; Cl, 12.84. Found: C, 62.98; H, 4.26; N, 2.62; Cl, 12.92.

In a similar manner *o*-tolualdehyde mustard gave an 84% yield of solid, m.p. 180–181° (for absolute ethanol).

Anal. Calcd. for $C_{30}H_{25}Cl_2NO_6$: C, 63.61; H, 4.45; N, 2.47. Found: C, 63.61; H, 4.59; N, 2.45.

(9) G. Domagk, R. Behnisch, F. Mietzsch, and H. Schmidt, *Naturwiss.*, **33**, 315 (1946).

(10) W. R. Sullivan, C. F. Huebner, M. A. Stahmann, and K. P. Link, *J. Am. Chem. Soc.*, **65**, 2288 (1943).

(11) Analysis by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Drs. Weiler and Strauss, Oxford, England. All melting points are uncorrected.

(12) B. A. Gingras, R. W. Hornal, and C. H. Bayley, *Canadian J. Chem.*, **38**, 712 (1960).

(13) In cases where 80 ml. of hot ethanol would not dissolve the material the aldehyde solution was added to a suspension.

Microbiological Transformation of Strophanthidin[1]

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During the past few years, reports have appeared on the microbiological transformation of the cardiac aglycones digitoxigenin,[2–10]