TABLE III

Compd	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	I, % Calcd	I, % Found	N, % Calcd	N, % Found	S, % Calcd	S, % Found	Recrystn solvent	Uv data $\lambda_{max}^{0.1\ N\ HCl}$, mμ (ε)
IUdR 3′-sulfate	$C_9H_{10}IKN_2O_8S$[a]	22.89	22.69	2.13	2.35	26.87	26.63	5.93	5.68	6.79	7.00	H_2O–EtOH	286 (6830)
IUdR 5′-sulfate	$C_9H_{10}IKN_2O_8S$	22.89	22.85	2.13	2.30	26.87	27.18	5.93	6.15	6.79	6.84	H_2O–EtOH	288 (7015)
IUdR disulfate	$C_9H_9IK_2N_2O_{11}S_2$	18.31	18.02	1.54	1.88	21.49	20.96	4.74	4.70	10.86	10.97	H_2O–EtOH	288 (7019)
ICdR 3′-sulfate	$(C_9H_{11}IN_3O_7S)_2Ba$[a]	21.58	21.73	2.21	2.49	25.34	25.21	8.40	8.18	6.40	6.20	H_2O	308 (8130)
ICdR 5′-sulfate	$(C_9H_{11}IN_3O_7S)_2Ba$	21.58	21.34	2.21	2.37	25.34	25.08	8.40	8.18	6.40	6.29	H_2O–EtOH	308 (7890)
ICdR disulfate	$C_9H_{10}IK_2N_3O_{10}S_2$	18.34	18.49	1.70	2.12	21.53	20.85	7.13	7.05	10.88	10.57	H_2O	308 (8570)

[a] The analytical sample was prepared from the 3′-sulfate obtained *via* the 5′-trityl intermediate.

Anal. Calcd for $C_{28}H_{33}IN_3O_4$: C, 56.47; H, 4.40; I, 21.35; N, 7.06. Found: C, 56.54; H, 4.49; I, 21.20; N, 6.89.

5-Iododeoxyuridine 3′-Sulfate.—A mixture of 5′-trityl-5-iododeoxyuridine (1.2 g, 2 mmoles) and pyridine–sulfur trioxide (0.476 g, 2.8 mmoles) in dry pyridine (8 ml) was stirred at 28° for 48 hr. The reaction was terminated with H_2O (40 ml) and allowed to stand overnight at 0°. The mixture, after concentration to dryness *in vacuo* at 40°, was dissolved in methanol (20 ml) and again concentrated to dryness *in vacuo* at 40°; this operation was repeated several times. The powdery residue was dissolved in 80% aqueous acetic acid (30 ml) and the solution was stirred for 2 hr at 45°. The solvent was removed *in vacuo* at 40° and the residue was taken up in H_2O (30 ml). 5-Iododeoxyuridine 3′-sulfate (1.6 mmoles, 78%), separated by paper chromatography in isobutyric acid–H_2O–concentrated NH_4OH (66:33:1), was converted to the potassium salt *via* Dowex 50 (K^+ form). Its infrared spectrum, R_f, and ultraviolet spectra were identical with those of the potassium salt of fraction A (Table I).

5-Iododeoxycytidine 3′-Sulfate.—5′-O-Trityl-5-iododeoxycytidine was treated with PST, according to the procedure for 5-iododeoxyuridine 3′-sulfate, to give 5-iododeoxycytidine 3′-sulfate in 82% yield. Its barium salt had the same R_f value, as well as infrared and ultraviolet spectra, as the barium salt of fraction A′ (Table I).

3′-O-Acetyl-5-iododeoxyuridine.—To a cooled solution of 5′-O-trityl-5-iododeoxyuridine (4.8 g, 8 mmoles) in dry pyridine (40 ml) was added acetic anhydride (1.8 ml) at 0° with stirring. The solution, after stirring an additional 24 hr at room temperature, was poured into ice–water (15 ml) and the solvent was removed *in vacuo* at 40°. The residue was dissolved in 80% aqueous acetic acid (100 ml); after stirring at 45° for 54 hr, the solution was stored at 4° for 12 hr and the separated triphenylcarbinol was removed by filtration. The filtrate was concentrated to dryness *in vacuo* at 40° to yield the crude 3′-O-acetyl derivative (2.5 g), which was washed (CCl_4) and recrystallized from methanol and petroleum ether (bp 30–60°). The analytical sample was recrystallized from ethyl acetate and petroleum ether; mp 196°, $\lambda_{max}^{95\%\ EtOH}$ 283 mμ (7600).

Anal. Calcd for $C_{11}H_{13}IN_2O_6$: C, 33.35; H, 3.31; I, 32.03; N, 7.06. Found: C, 33.09; H, 3.52; I, 32.15; N, 7.25.

Potential Carcinostatic Agents. I. Derivatives and Analogs of 1-(2-Hydroxyethyl)-3-(4-tolyl)urea

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During the course of a program for synthesizing a group of substituted ureas designed as potential herbicides to be evaluated in our greenhouse, we also submitted these to the Cancer Chemotherapy National Service Center for antitumor screening. One of these, the title compound, showed some activity against Sarcoma 180 in mice and it was decided to synthesize a number of derivatives and analogs of this compound, not already reported and tested,[1] for similar screening. One of these derivatives, 1-(2-chloroethyl)-1-nitroso-3-(4-tolyl)urea, was particularly active against L1210 lymphoid leukemia in two types of mice. Table I lists these substances and their physical properties. They were made by literature procedures, as outlined for typical cases in the Experimental Section.

Biological Data.—Although several of these compounds passed stage I or stage II in the Lewis lung carcinoma test, they did not have confirmed activity. 1-(2-Hydroxyethyl)-3-(4-tolyl)urea had confirmed activity against Sarcoma 180, but was inactive in the lymphoid leukemia (L1210) test. 1-(2-Hydroxyethyl)-1-nitroso-3-(4-tolyl)urea showed slight activity against L1210 (T/C = 100–125% in the multiple-dose assay). However, 1-(2-chloroethyl)-1-nitroso-3-(4-tolyl)urea had considerable activity (L1210); see Table II.

Experimental Section[2]

Method A. 1-(2-Hydroxyethyl)-3-(4-tolyl)urea.—A stirred suspension of 2-aminoethanol (6 g, 0.98 mole) in toluene (100 ml) was treated at room temperature with *p*-tolyl isocyanate (13 g, 0.098 mole). After stirring for 4 hr the product was collected on a filter and washed with toluene and then with ligroin (bp 60–70°).

Method B. 1-(2-Chloroethyl)-3-(4-tolyl)urea.—A stirred solution of *p*-toluidine (10.5 g, 0.098 mole) in toluene (100 ml) was treated with 2-chloroethyl isocyanate (10 g, 0.098 mole) at room temperature. After stirring for 2 hr the product was collected on a filter and washed with toluene and then ligroin. The product was recrystallized from acetonitrile.

Method C.[1b] **1-(2-Chloroethyl)-1-nitroso-3-(4-tolyl)urea.**—A stirred solution of 1-(2-chloroethyl)-3-(4-tolyl) urea (7 g, 0.033 mole) in 300 ml of 98% formic acid (5–7°) was treated with dry $NaNO_2$ (6 g, 0.09 mole) in small portions over a period of 1.5 hr. The solution was stirred for an additional hour (0–5°) and 175 ml of ice water was then added slowly. The mixture was stirred an additional 30 min at 0°. The light yellow crystalline product was collected on a filter, washed with cold water, and dried (P_2O_5, under vacuum).

Method D. 1-(2-Iodoethyl)-3-(4-tolyl)urea.—1-(2-Chloroethyl)-3-(4-tolyl)urea (6 g, 0.06 mole) was refluxed with anhydrous NaI[3] (9 g, 0.06 mole) in 50 ml of dry acetone for 24 hr ($CaCl_2$ drying tube). The solution was then filtered hot to remove any salts and the filtrate was diluted with 500 ml of cold water. The white precipitate that formed was collected on a filter, washed with water, and dried. The product was recrystallized from acetonitrile.

Method E. 1-(2-Bromoethyl)-3-(4-tolyl)urea.—1-(2-Hydroxyethyl)-3-(4-tolyl)urea (26 g, 0.144 mole) was added slowly with stirring to 40 ml of PBr_3 at room temperature. After the addition, the reaction mixture was heated on a hot-water bath and stirred for 3 hr. During this time, an orange suspension formed.

(1) (a) For example, T. P. Johnston, G. S. McCaleb, and J. A. Montgomery, *J. Med. Chem.*, **6**, 669 (1963); (b) T. P. Johnston, G. S. McCaleb, P. S. Opliger, and J. A. Montgomery, *ibid.*, **9**, 892 (1966).

(2) Melting points were taken on a Fisher-Johns block and are corrected to standards.

(3) The NaI was heated strongly (~300°) on a hot plate just prior to use.

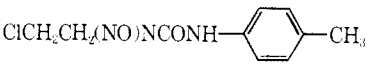
TABLE I

N-ARYL-N'-(ω-SUBSTITUTED-ALKYL)UREAS AND THEIR N'-NITROSO DERIVATIVES

Ar	Method of synthesis	Recrystn solvent[a]	Yield, %	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Halogen, % Calcd	Halogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
(2-Hydroxyethyl)ureas, ArNHCONHCH$_2$CH$_2$OH													
p-Tolyl	A	A	80	151–153	$C_{10}H_{14}N_2O_2$	61.83	61.78	7.27	7.20			14.42	14.53
m-Tolyl	A	N	94	106.5–108.5	$C_{10}H_{14}N_2O_2$	61.83	62.04	7.27	7.28			14.42	14.60
o-Methoxyphenyl	A	A	78	103.5–105	$C_{10}H_{14}N_2O_3$	57.13	57.18	6.71	6.68			13.33	13.48
3,4-Dichlorophenyl	A	N	80	136.5–138.5[b]	$C_9H_{10}Cl_2N_2O_2$	43.39	43.47	4.05	4.15	28.46	28.37	11.25	11.42
(2-Hydroxyethylnitroso)urea, ArNHCON(NO)CH$_2$CH$_2$OH													
p-Tolyl	C	N	96	75 dec	$C_{10}H_{13}N_3O_3$	53.80	53.88	5.87	5.85			18.83	18.90
(2-Chloroethyl)ureas, ArNHCONHCH$_2$CH$_2$CH$_2$Cl													
p-Tolyl	B	A	85	178–179[c]	$C_{10}H_{13}ClN_2O$	56.47	56.59	6.18	6.20	16.67	16.66	13.17	13.05
m-Tolyl	B	A	78	123.5–125	$C_{10}H_{13}ClN_2O$	56.47	56.77	6.18	6.34	16.67	16.83	13.17	13.26
o-Methoxyphenyl	B	A	70	118.5–120	$C_{10}H_{13}ClN_2O_2$	52.52	52.46	5.73	5.77	15.50	15.55	12.25	12.23
3,4-Dichlorophenyl	B	A	32	125.5–127	$C_9H_{10}Cl_3N_2O$	40.40	40.41	3.39	3.42	39.75	39.52	10.47	10.96
p-Bromophenyl	B	A	84	181–183	$C_9H_{10}BrClN_2O$	38.94	38.66	3.63	3.81	12.77[e] 28.71[f]	12.93[e] 28.91[f]	10.09	10.16
(2-Chloroethylnitroso)ureas, ArNHCON(NO)CH$_2$CH$_2$Cl													
p-Tolyl	C	N	78	88–89.5	$C_{10}H_{12}ClN_3O_2$	49.70	49.48	5.00	4.76	14.67	14.69	17.39	17.23
m-Tolyl	C	N	79	100–100.5	$C_{10}H_{12}ClN_3O_2$	49.70	49.54	5.00	5.31	14.67	14.60	17.39	17.20
o-Methoxyphenyl	C	N	76	75–80 dec	$C_{10}H_{12}ClN_3O_3$	46.61	46.53	4.69	4.73	13.76	13.86	16.31	16.15
3,4-Dichlorophenyl	C	N	92	109.5–110	$C_9H_9Cl_2N_3O_2$	36.45	36.41	2.72	2.86	35.87	35.64	14.17	13.99
p-Bromophenyl	C	N	92	90–90.5	$C_9H_9BrClN_3O_2$	35.26	35.02	2.96	3.09	11.58[e] 26.07[f]	11.43[e] 26.13[f]	13.71	13.83
(2-Bromoethyl)urea, ArNHCONHCH$_2$CH$_2$Br													
p-Tolyl[d]	E	T	37	161–163	$C_{10}H_{13}BrN_2O$	46.71	46.66	5.09	4.98	31.08	31.33	10.90	10.81
(2-Bromoethylnitroso)urea, ArNHCON(NO)CH$_2$CH$_2$Br													
p-Tolyl	C	N	69	102–102.5	$C_{10}H_{12}BrN_3O_2$	41.98	41.80	4.23	4.32	27.93	27.96	14.69	14.60
(2-Iodoethyl)urea, ArNHCONHCH$_2$CH$_2$I													
p-Tolyl	D	A	31	180–182	$C_{10}H_{13}IN_2O$	39.49	39.78	4.27	4.19			9.21	8.98
(3-Hydroxypropyl)urea, ArNHCONHCH$_2$CH$_2$CH$_2$OH													
p-Tolyl	A	W	59	138–139	$C_{11}H_{16}N_2O_2$	63.44	63.44	7.74	7.74			13.45	13.39
(3-Chloropropyl)urea, ArNHCONHCH$_2$CH$_2$CH$_2$Cl													
p-Tolyl	F	A	35	126.5–127.5	$C_{11}H_{15}ClN_2O$	58.28	58.41	6.67	6.76	15.64	15.49	12.36	12.48
(3-Chloropropylnitroso)urea, ArNHCON(NO)CH$_2$CH$_2$CH$_2$Cl													
p-Tolyl	C	N	98	89.5–90	$C_{11}H_{14}ClN_3O_2$	51.67	51.58	5.52	5.54	13.86	13.77	16.44	16.63

[a] A, acetonitrile; N, none; T, toluene; W, water. [b] N. E. Good (*Plant Physiol.*, **36**, 788 (1961)) reported mp 137–138°. [c] J. P. Picard and A. F. McKay (*Can. J. Chem.*, **31**, 896 (1953)) and H. Najer and R. Gindicelli (*Bull. Soc. Chim. France*, 1650 (1960)) reported mp 178–179°. [d] F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957). [e] Chlorine analysis. [f] Bromine analysis.

TABLE II: *In Vivo* TESTING AGAINST L1210 OF



Dose, mg/kg, BDF$_1$ mice	Survivors	T/C, %[a]
200	4/4	<100
400	4/4	<100
100	4/4	86
50	4/4	197
75	4/4	118
50	4/4	171
33	4/4	152
22	4/4	161
25	6/6	152
15	6/6	206[b]
9	6/6	165
5.2	6/6	169
4	5/6	<100
2	6/6	129
1	6/6	107
0.5	6/6	103
CDF$_1$ mice		
25	6/6	87
15	6/6	193
9	6/6	189
5.4	6/6	136

[a] Test/control: days survived (as per cent). [b] Four cures.

The excess PBr_3 was then distilled under vacuum and the resulting orange paste was poured over ice. The suspension was collected on a filter and dried under vacuum over P_2O_5. The product was then extracted with three 250-ml portions of boiling toluene. The extracts were filtered and combined and the product was allowed to crystallize.

Method F. 1-(3-Chloro-*n*-propyl)-3-(4-tolyl)urea.—1-(3-Hydroxy-*n*-propyl)-3-(4-tolyl)urea (21 g, 0.10 mole) was added slowly to freshly distilled $POCl_3$ on a warm-water (60°) bath. The reaction mixture was then heated by use of a boiling-water bath for 1.5 hr. After cooling to room temperature, the mixture was poured over crushed ice with stirring. NH_4OH was slowly added with stirring until the pH was slightly above 7. The syrupy material was cooled in an ice bath until it had solidified and was then collected and dried under vacuum over P_2O_5. It was then extracted with boiling benzene, crystallized, filtered off, and recrystallized from acetonitrile.

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