TABLE II
ANTITUMOR ACTIVITY OF CERTAIN OCTADECYLTHIOSEMICARBAZONES AGAINST SARCOMA 180, ADENOCARCINOMA 755, AND LEUKEMIA 1210

Derivative	Dose, mg./kg.	Survivors	Change in weight, g., test/control	Tumor wt., mg., test/control	T/C, %
		Sarcoma 180			
2,4-Dichlorobenzaldehyde	350	3/6	−04.0/−00.2	146/863	Toxic
	175	6/6	−03.7/00.1	377/1109	33
	175	5/6	−04.7/−00.4	218/665	32
	175	5/6	−02.3/00.1	415/905	45
	175	6/6	−03.5/−00.3	195/764	25
	130	4/6	−05.1/00.8	233/913	25
	130	6/6	−02.8/00.2	435/1002	43
	130	4/6	−03.8/−00.2	336/943	35
	90	6/6	−03.8/−00.2	430/943	45
	60	5/6	−03.1/−00.2	425/943	45
4-Cyanobenzaldehyde	500	6/6	01.1/−00.6	538/1227	43
	250	6/7	−04.7/−03.7	545/1209	45
		Adenocarcinoma 755			
3,4-Dichlorobenzaldehyde	225	9/10	−01.2/01.4	421/1493	28
	225	10/10	−01.6/02.4	1067/1587	67
2,4-Di-*t*-butyl-5-methoxybenzaldehyde	450	7/10	−05.1/00.5	368/964	38
4-Dimethylaminobenzaldehyde	175	7/10	−01.6/01.2	557/1075	51
	175	7/10	−01.9/01.6	420/1294	32
	175	10/10	−04.2/−01.1	536/1057	50
	175	5/10	00.3/02.2	565/1086	53
	175	5/10	−02.4/00.2	273/946	28
	175	7/10	−00.7/00.2	850/1079	78
		Leukemia 1210			
Valeraldehyde	450	6/6	−01.9/01.5	10.3/7.9	1.30
	450	6/6	−00.7/02.7	11.6/9.2	1.26
	675	6/6	−01.9/01.7	9.1/10.1	0.90
	450	6/6	−01.5/01.7	9.6/10.1	0.95
	300	6/6	−00.6/01.7	10.5/10.1	1.03
	200	6/6	−00.2/01.7	9.5/10.1	0.94

In the light of the results with the 2,4-dichlorobenzaldehyde derivative, a test of its effectiveness in clinical trials is indicated.

Antiviral Activity of 2,4-Dichlorobenzaldehyde-4-octadecyl-3-thiosemicarbazone.[10]—Since this compound has shown confirmed activity in the S-180 mouse tumor system, it was decided to test the substance for antiviral activity before undertaking a test of all the compounds in the series. Preliminary experiments for antiviral activity of the compound against experimental poliomyelitis in mice were carried out as follows. A group of 38 Swiss white mice were fed the drug for 8 days at a daily dose of 0.5 g./kg. of body weight. On the second day of feeding, these mice along with 38 untreated controls were challenged intracerebrally with $10^{5.5}$ $TCID_{50}$ of Type I poliovirus, L Sa strain. The paralytic rates were 42 and 60.5% in the treated and control groups, respectively. The same type of experiment was repeated but the treatment with the drug started 5 days before virus infection and stopped 2 days afterwards. Here the death rate was 30% for the treated and 47.5% for the controls. In both trials, the difference between the treated and controls seemed to be more marked in the early course of infection (Fig. 1, third and fourth day).

(10) Dr. Y. T. Chang of the Laboratory of Pharmacology and Toxicology, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, studied the compound for its effect on rat leprosy in mice and found it to be inactive as a leprocidal agent.

New Compounds

Nucleosides. IV. 1-(2-Deoxy-β-D-lyxofuranosyl)-5-iodouracil[1]

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Recently, syntheses were described for the conversion of thymidine[2,3] and 5-fluoro-2′-deoxyuridine[3] to the corresponding 2-deoxylyxosyl (-xylosyl) epimers *via* 2,3′-anhydronucleoside intermediates. In view of the marked antiviral activity[4-8] of 5-iodo-2′-deoxyuridine, it appeared of interest to extend these methods to the synthesis of 1-(2-deoxy-β-D-lyxofuranosyl)-5-iodouracil (IV).

(1) This work was supported in part by research grants CY-2903 and CY-5943 from the National Cancer Institute, Public Health Service, and in part by an institutional grant from the United Foundation of Greater Detroit allocated through the Michigan Cancer Foundation.

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(8) R. J. Huebner, A. D. Welch, P. Calabresi, and W. H. Prusoff, *Proc. Assoc. Cancer Res.*, **4**, 30 (1963).

Experimental[9]

1-(2-Deoxy-5-*O*-trityl-β-D-lyxosyl)uracil (II).—To a cooled solution of 1.73 g. (3.68 mmoles) of 5′-*O*-trityl-2′-deoxyuridine[10] (I) in 10 ml. of dry pyridine was added 0.57 ml. (7.36 mmoles) of methanesulfonyl chloride and the mixture held at 5° for 16 hr. Water (2.0 ml) was added and, after 0.5 hr. at room temperature, the reaction mixture was poured into 500 ml. of stirred ice-water. The off-white solid was collected and washed with generous quantities of water. The air-dried product was dissolved in 80 ml. of 50% ethanol that contained 14.5 ml. of *N* sodium hydroxide and the solution was refluxed for 4 hr. The volume was then reduced *in vacuo* to *ca.* 40 ml.; the reaction mixture was then chilled and carefully acidified (pH 2) with dilute hydrochloric acid. The gelatinous product was collected, washed with water, and sucked dry. The dry product was readily transformed to a crystalline solid on stirring with 50 ml. of ethanol at room temperature for 0.5 hr., wt. 1.64 g. (95% yield), m.p. 225–228°. Two recrystallizations from ethanol provided an analytical sample, m.p. 239–240°, $[\alpha]^{25}D$ −14.9° (*c* 0.93, DMF); λ_{max}^{EtOH} 262 mμ (ε 10,630), and λ_{min} 243 mμ (ε 6370).

Anal. Calcd. for $C_{28}H_{26}N_2O_5$: C, 71.47; H, 5.57; N, 5.96. Found: C, 71.30; H, 5.73; N, 5.69.

1-(2-Deoxy-β-D-lyxofuranosyl)uracil (III).—A solution of 1.45 g. (3.08 mmoles) of II in 10 ml. of 80% acetic acid was refluxed for 10 min. The reaction mixture was evaporated to dryness *in vacuo* and the residue was evaporated from three 10-ml. portions of ethanol. The product crystallized from methanol–ethyl acetate, 0.58 g. (two crops, 83% yield), m.p. 163–165°. A second recrystallization from methanol failed to alter the melting point; $[\alpha]^{25}D$ +58.2 (*c* 0.55, ethanol); in H_2O, λ_{max} 263 mμ (ε 10,620), and λ_{min} 232 mμ (ε 2760); 0.1 *N* HCl, λ_{max} 262 mμ (ε 9610), and λ_{min} 231 mμ (ε 2220); 0.1 *N* NaOH, λ_{max} 262 mμ (ε 7070), add λ_{min} 241 mμ (ε 4520).

Anal. Calcd. for $C_9H_{12}N_2O_5$: C, 47.36; H, 5.30; N, 12.28. Found: C, 47.22; H, 5.40; N, 12.09.

1-(2-Deoxy-β-D-lyxofuranosyl)-5-iodouracil (IV).[11]—A mixture of 0.25 g. (1.1 mmoles) of III, 0.25 g. (1 mmole) of iodine, 2.5 ml. of *N* nitric acid, and 1.3 ml. of chloroform was refluxed for 2 hr. On cooling, a colorless crystalline solid was deposited. The product was collected, washed free of iodine with ether, and recrystallized from water, 0.23 g. (57% yield), m.p. 180–181° dec., $[\alpha]^{25}D$ −4.9° (*c* 0.81, ethanol); in H_2O, λ_{max} 289 mμ (ε 6530) and λ_{min} 247 mμ (ε 970); 0.1 *N* HCl, λ_{max} 288 (ε 4330), and 255 mμ (ε 2010); 0.1 *N* NaOH, λ_{max} 278 mμ (ε 5310) and λ_{min} 254 mμ (ε 2830).

Anal. Calcd. for $C_9H_{11}IN_2O_5$: C, 30.52; H, 3.13; I, 35.84; N, 7.91. Found: C, 30.28; H, 2.88; I, 35.70; N, 8.09.

(9) Melting points are corrected. Ultraviolet spectra were recorded by a Cary Model 11 spectrophotometer. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(10) J. Smrt and F. Sorm, *Collection Czech. Chem. Commun.*, **25**, 553 (1960); *Chem. Abstr.*, **54**, 12145 (1960).

(11) This procedure is identical with that described by W. H. Prusoff. *Biochim. Biophys. Acta*, **32**, 295 (1959), for the preparation of 5-iodo-2′-deoxyuridine.

5-Aryl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-ones

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Because of our interest in 1,4-benzodiazepin-2-ones[1] and 3,1,4-benzoxadiazepin-2(1*H*)ones,[2] it seemed desirable to prepare some aza analogs of these ring systems. Accordingly, several 5-aryl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-ones have been prepared by two related methods, as shown in the reaction scheme.

(1) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).

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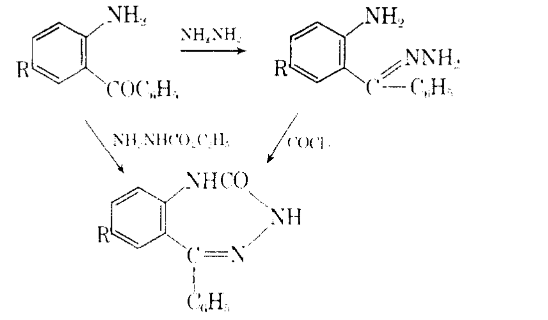

Experimental

5-Phenyl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-one.—A solution of 12 g. of 12.5% phosgene in benzene was added dropwise to a cooled solution of 3.2 g. of 2-aminobenzophenone hydrazone and 5 ml. of triethylamine in 50 ml. of benzene. After addition was completed, the mixture was stirred at room temperature for 1 hr. After separating the triethylamine hydrochloride by filtration, the solution was evaporated to dryness *in vacuo.* Recrystallization of the residue from ethanol afforded 1.4 g. of product, m.p. 238°.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.68; N, 17.70. Found: C, 70.69; H, 4.53; N, 18.04.

7-Methyl-5-phenyl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-one, m.p. 253–255°, was prepared similarly from 2-amino-5-methylbenzophenone hydrazone in a yield of 50%.

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.61; H, 5.43; N, 16.64.

7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-one.—A mixture of 5 g. of 2-amino-5-chlorobenzophenone and 5 ml. of ethyl hydrazinecarboxylate was heated at 190° for 1 hr. The mixture was cooled and dissolved in 75 ml. of ethanol. On standing there was obtained 1.6 g. of product, m.p. 246–248°.

Anal. Calcd. for $C_{14}H_{10}ClN_3O$: C, 61.89; H, 3.72; Cl, 13.05; N, 15.47. Found: C, 61.65; H, 3.72; Cl, 13.27; N, 15.18.

Concentration of the mother liquor afforded 0.5 g. of 2-amino-5-chlorobenzophenone hydrazone ethyl carboxylate, m.p. 209°.

Anal. Calcd. for $C_{16}H_{16}ClN_3O_2$: C, 60.47; H, 5.07; Cl, 11.16; N, 13.23. Found: C, 60.16; H, 5.07; Cl, 11.25; N, 13.04.

Quinazolines and 1,4-Benzodiazepines. XIX.[1] N-Alkyl Derivatives of Substituted 1,3,4,5-Tetrahydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones

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As a continuation of our investigation on psychotherapeutic agents of the 1,4-benzodiazepine class of compounds, we have prepared a series of 1,3,4,5-tetrahydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones and from these compounds a number of N-alkyl derivatives. For the sake of simplicity, the Experimental section of this paper will concern itself with the chemistry of only one of these compounds, namely, 7-chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one and its N-methyl derivatives. As shown in the Experimental, because of the difference in basicity between the two nitrogen atoms, we found it possible to alkylate the 1-nitrogen independently of the 4-nitrogen and *vice versa.* All other compounds and derivatives prepared by the same procedures will be found in Table III.

(1) Paper XVIII: L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964).