It has been shown[12] that, within a series of lysergic acid derivatives, there is a marked parallelism between ability to produce a rise in the body temperature of rabbits and psychotomimetic activity in man. There has also been a suggestion[10] that the pyrogenic potency in rabbits of some simple tryptamines may parallel their ability to produce behavioral changes in rats. The nine indoles examined during this investigation only produced rises in rabbit rectal temperature at toxic dose levels. 5-Aminomethyl-2,3-dimethylindole did not affect rectal temperature at any dose level and so it seems improbable that the effect of this compound in the open field test was due to any psychotomimetic activity.

Among such relatively inactive compounds it is impossible to speculate concerning structure–activity relationships.

Experimental Section[13]

Ethyl 2,3-dimethylindole-4-, -5-, -6-, and -7-carboxylates were obtained by esterification of the appropriate indolecarboxylic acid prepared by the method reported by Brown, *et al.*[6]

2,3-Dimethylindole-5-carboxamide (VI).—A mixture of 2,3-dimethylindole-5-carboxylic acid (14 g), PCl_5 (19 g), and dry ether (350 ml) was stirred at room temperature for 18 hr and then filtered. The filtrate was concentrated to about 100 ml, petroleum ether (bp 40–60°) (1400 ml) was added, and the mixture again was filtered. The filtrate was refrigerated for 24 hr. The crystalline material which had separated was collected and then added to ethanol (30 ml) and saturated with NH_3 and the mixture was left at room temperature for 8 hr. The ethanol was removed by distillation and water was added to the residue yielding 2.5 g of crude VI, mp 176–178°. A further 2 g of crude product was obtained by passing NH_3 through the petroleum ether (bp 40–60°) filtrate; yield 4.5 g (32%). An analytical sample was obtained by recrystallization from ethyl acetate–petroleum ether (bp 60–80°), mp 182–183°, lit.[8] 170–172°.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.23; H, 6.51; N, 15.03.

2,3-Dimethylindolecarboxhydrazides (Table I, Procedure A).—The ethyl 2,3-dimethylindolecarboxylate (15.6 g, 0.07 mole) was refluxed with hydrazine hydrate (100 ml, 99–100%) for 2 hr. The reaction mixture was distilled under reduced pressure to remove some of the excess of hydrazine hydrate and then cooled. The precipitated hydrazide was collected by filtration, washed with water, and dried.

2,3-Dimethylindolecarboxamides (Table I, Procedure B).—Sodium nitrite (2 g, 0.029 mole) in water (20 ml) was added to a stirred, cold (0–5°) solution of the indolecarboxhydrazide (5.7 g, 0.028 mole) in glacial acetic acid (300 ml), and the mixture was stirred at 0–5° for 30 min. Water (1 l.) was added to the reaction mixture and the precipitated azide was collected, washed with water, and dried. The crude azide was then added to an excess of the appropriate amine (1 mole) at 0°, and the mixture was stirred at this temperature for 3 hr and added to water (400 ml). The precipitated amide was collected by filtration.

Preparation of the Amines (Table I, Procedure C).—The amines were prepared by adding a solution of the appropriate carboxhydrazide or carboxamide (0.03 mole) in dry dioxane (500 ml) to a stirred, refluxing suspension of $LiAlH_4$ (0.2 mole) in dry dioxane (150 ml) and refluxing the resultant mixture for 4 hr.

(12) A. Hofmann, *Svensk Kem. Tidskr.*, **72**, 12 (1960).

(13) Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus.

Hexahydropyrimidines. VII.[1] A Study of 2-Substituted 1,3-Bis(2-hydroxy-3-methoxybenzyl)hexahydropyrimidines and 2-Substituted 1,3-Bis(3,4-dimethoxybenzyl)hexahydropyrimidines as Antitumor Agents[2]

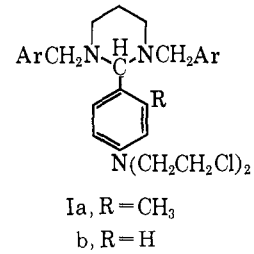
JOHN H. BILLMAN AND M. SAMI KHAN

Department of Chemistry, Indiana University, Bloomington, Indiana

Received December 9, 1965

A series of 2-substituted 1,3-bis(2-hydroxy-3-methoxybenzyl)hexahydropyrimidines and 2-substituted 1,3-bis(3,4-dimethoxybenzyl)hexahydropyrimidines have been prepared and screened for antitumor activity. The tested compounds displayed no significant antineoplastic activity in tissue culture or animal studies.

In a previous study from this laboratory,[3] the synthesis and antitumor activity of a series of 1,2,3-substituted hexahydropyrimidines of the general structure I have been reported. One of these compounds, 2-{4-[N,N-Bis(2-chloroethyl)amino]-2-methylphenyl}-1,3-bis(*p*-methoxybenzyl)hexahydropyrimidine (Ia), exhibited appreciable amount of antitumor activity against Walker carcinoma 256 in preliminary test studies. A wide range of activity was observed by varying the substituents Ar in the structure Ia from *p*-methoxyphenyl (100% inhibition at 100 mg/kg) to *p*-chlorophenyl (71% inhibition at 100 mg/kg) to 2,4-dichlorophenyl (22% inhibition at 100 mg/kg). These substituents established the same relative order of activity in the Ib series. The markedly increased antitumor activity



Ia, R = CH_3
b, R = H

thus appeared to be related to the electron-donating ability of the substituents on N-1 and N-3 of the hexahydropyrimidine ring, although this ring is well separated from the nitrogen mustard group. Therefore, structure–activity relationship can be drawn.

The mechanism by which compounds of type II act in the biological systems is not well understood at this time. An attempt is, however, being made to determine whether the molecule as a whole is the effective

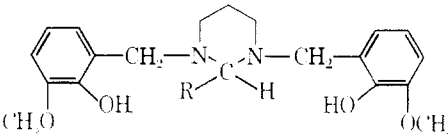
(1) Part VI: J. H. Billman and J. L. Meisenheimer, *J. Med. Chem.*, **8**, 540 (1965).

(2) This investigation was supported by a Public Health Service Research Grant No. CA-07227-02 from the National Cancer Institute.

(3) J. H. Billman and J. L. Meisenheimer, *J. Med. Chem.*, **7**, 115 (1964).

TABLE I

2-SUBSTITUTED 1,3-BIS(2-HYDROXY-5-METHOXYBENZYL)HEXAHYDROPYRIMIDINES

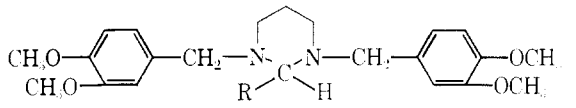


No.	R	Yield, % (pure)	Mp, °C (cor)	Formula	Nitrogen, %—Calcd	Nitrogen, %—Found
1	H[a]	98.6	171–172	$C_{26}H_{26}N_2O_4$	7.82	7.87
2	*n*-Hexyl[b]	98.4	90–91	$C_{26}H_{38}N_2O_4$	6.33	6.34
3	Phenyl[b]	70.2	121–122	$C_{26}H_{30}N_2O_4$	6.44	6.52
4	*o*-Hydroxyphenyl[b]	99.9	163–164	$C_{26}H_{30}N_2O_5$	6.21	6.06
5	2-Hydroxy-3-methoxyphenyl[b]	98.9	92–93	$C_{27}H_{32}N_2O_6$	5.82	5.71
6	*p*-Dimethylaminophenyl[b]	97.4	145–146	$C_{28}H_{35}N_3O_5$	8.79	9.00
7	2,3-Dimethoxyphenyl[c]	91.0	147–148	$C_{28}H_{34}N_2O_6$	5.66	5.79
8	4-[N,N-Bis(2-chloroethyl)amino]phenyl[d]	80.0	103–104	$C_{30}H_{37}Cl_2N_4O_4$	7.31	7.27
9	4-[N,N-Bis(2-chloroethyl)amino]-2-methylphenyl[d]	90.0	95–96	$C_{31}H_{39}Cl_2N_3O_5$	7.14	7.30
10	4-[N,N-Bis(2-chloroethyl)amino]-2-chlorophenyl[e]	83.3	136–137	$C_{30}H_{36}Cl_3N_3O_4$	6.95	7.26

[a] Recrystallized from ethanol–acetonitrile (2:1). [b] Recrystallized from ethanol. [c] Recrystallized from ethanol–benzene (1:1). [d] Recrystallized from acetonitrile. [e] Recrystallized from ethanol–acetonitrile (1:1).

TABLE II

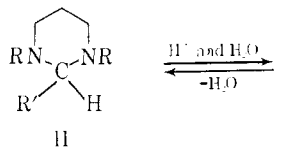
2-SUBSTITUTED 1,3-BIS(3,4-DIMETHOXYBENZYL)HEXAHYDROPYRIMIDINES



No.	R	Yield, % (pure)	Mp, °C (cor)	Formula	Nitrogen, %—Calcd	Nitrogen, %—Found
11	*n*-Hexyl[a]	79.6	73–74	$C_{28}H_{42}N_2O_4$	5.94	6.09
12	Phenyl[b]	75.7	119.5–120.5	$C_{28}H_{34}N_2O_4$	6.05	5.95
13	*o*-Hydroxyphenyl[a]	78.1	135–136	$C_{28}H_{34}N_2O_5$	5.85	6.01
14	2-Hydroxy-3-methoxyphenyl[a]	80.7	114.5–115.5	$C_{29}H_{36}N_2O_6$	5.51	5.78
15	*p*-Dimethylaminophenyl[c]	72.3	144–145	$C_{30}H_{39}N_3O_4$	8.30	8.12
16	4-[N,N-Bis(2-chloroethyl)amino]phenyl[b]	82.9	56–57.5	$C_{32}H_{41}Cl_2N_3O_4$	6.97	7.00
17	4-[N,N-Bis(2-chloroethyl)amino]-2-methylphenyl[b]	83.4	101–102	$C_{33}H_{43}Cl_2N_3O_4$	6.80	6.79
18	4-[N,N-Bis(2-chloroethyl)amino]-2-chlorophenyl[d]	86.3	130–131	$C_{32}H_{40}Cl_3N_3O_4$	6.59	6.57

[a] Recrystallized from ethanol. [b] Recrystallized from methanol. [c] Recrystallized from methanol–benzene (2:1). [d] Recrystallized from ethanol–acetonitrile (2:1).

agent or one of its breakdown products which might be formed by acid or enzymatic cleavage or possibly a combination of both. It has been suggested[3–5] that hexahydropyrimidines may be regarded as potential aldehydes, since, *in vitro*, they readily hydrolyze under mild acidic conditions to liberate free aldehydes and diamines, which in themselves may act as antitumor agents.



II

$$\text{II} \xrightleftharpoons[-H_2O]{H^+ \text{ and } H_2O} R'CHO + RNH(CH_2)_3NHR$$

III IV

R and R′ = H, alkyl, aryl, or aralkyl

In view of these encouraging results, the present investigation was prompted by the possibility that examination of a wide spectrum of 1,2,3-substituted hexahydropyrimidines having strongly electron-donating groups on N-1 and N-3 of the ring might lead to a more potent inhibitor of cancerous growth which in turn may help to shed more light on their behavior in the biological systems. Consequently, a series of hexahydropyrimidines were synthesized in an effort to obtain compounds with better therapeutic indices and to establish more fully their antitumor potentiality.

The hexahydropyrimidines summarized in Table I and II were prepared by allowing the desired aldehydes to react with secondary 1,3-diaminopropane of general structure VIII. Absolute ethanol was found to be much preferred for the ring closure reaction and provided colorless crystalline hexahydropyrimidines in high yields (70–99%). In general, the condensation proceeded smoothly and rapidly at room temperature or on heating at moderate temperature and in some cases solid product separated from the solution. The diamines employed in this project were obtained in two steps from trimethylenediamine and 2-hydroxy-3-

$$\underset{\text{V}}{2ArCHO} + \underset{\text{VI}}{H_2N(CH_2)_3NH_2} \xrightarrow{EtOH} [ArCH{=}NCH_2]_2CH_2 + 2H_2O$$

VII

$$\downarrow PtO_2\text{–}H_2$$

$$ArCH_2NH(CH_2)_3NHCH_2Ar$$

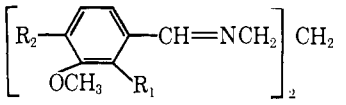
VIII

a, Ar = 2-hydroxy-3-methoxyphenyl
b, Ar = 3,4-dimethoxyphenyl

(4) J. H. Billman and J. L. Meisenheimer, *J. Med. Chem.*, **6**, 682 (1963).
(5) J. H. Billman and M. S. Khan, *ibid.*, **8**, 498 (1965).

TABLE III

ANTITUMOR SCREENING DATA FOR DI-SCHIFF BASE



R_1	R_2	Test system[a]	Dose, mg/kg	Survivors	Wt change (T − C),[b] g	Tumor wt[c] (T/C)[b]	% T/C[b]	ED_{50}, μg/ml
OH	H	KB						10
		DA	200	6/6	−11	10.0/10.0	100	
		LE	250	6/6	2	8.8/9.3	94	
		8P	250	10/10	−3	1709/2157	79	
H	CH_3O	SA	100	6/6	−11	1348/1395	96	

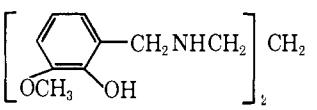
[a] KB, cell culture; DA, Dunning ascites leukemia; LE, Lymphoid leukemia L1210; 8P, P1798 lymphosarcoma; SA, sarcoma 180. [b] T stands for test animals, C for controls. [c] Tumor weight is in milligrams for SA and 8P, and grams for DA and LE.

methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde. In the initial step, the diamine VI was condensed with 2 moles of the required aldehyde V to produce the di-Schiff base VII. The reduction of the di-Schiff base with hydrogen over platinum oxide furnished the desired secondary 1,3-diaminopropane VIII.

Biological Results.—The hexahydropyrimidines, di-Schiff bases, and diamines listed in Tables I–IV were screened under the auspices of the Cancer Chemotherapy National Service Center (CCNSC) for antitumor activity, in doses up to 500 mg/kg and in cell culture tests. The screening results against various test systems are given in Tables III–V. All of these

TABLE IV

ANTITUMOR SCREENING DATA FOR DIAMINE



Test system[a]	Dose, mg/kg	Survivors	Wt change (T − C),[b] g	Tumor wt (T/C),[b] g	% T/C[b]
AA	100	3/3	−8		
	33	3/3	4		
	10	3/3	14		
	3	3/3	9		
WA	200	6/6	−10	8.6/8.3	103
	100	6/6	−50	8.3/8.3	100
	50	6/6	20	8.4/8.3	101
	25	6/6	30	9.5/8.3	114

[a] AA, toxicity text; WA, Walker 256. [b] T stands for test animals, C for controls.

compounds were nontoxic at high dose levels except compounds **11** and **13** (Table V). The test data indicate that none of these hexahydropyrimidines, di-Schiff bases, or diamines were active (by the criteria established by the CCNSC[6]) against Walker 256, Sarcoma 180, lymphoid leukemia L1210, Lewis lung carcinoma, solid Friend virus leukemia, Dunning ascites leukemia, and lymphosarcoma P1798 *in vivo* test systems. However, compound **17** (Table V) has given an ED_{50} value of 3.7μg/ml in a KB human epidermoid carcinoma and was active in cell culture test.

(6) *Cancer Chemotherapy Rept.*, **25**, 1 (1962). A compound is active against Walker 256 if it has a therapeutic index $TI \geq 4$ where $TI = LD_{10}/ED_{90}$. A compound is confirmed active in (a) KB cell culture if the average $ED_{50} \leq 4$ μg/ml for results from two laboratories; (b) Sarcoma 180, Lewis lung carcinoma, and solid Friend virus leukemia if the average $T/C \leq 42\%$ in three confirmation tests; and (c) lymphoid leukemia L1210 and Dunning ascites leukemia if $T/C \geq 125\%$ in a confirmation test.

Experimental Section

All melting points are corrected unless otherwise stated. The microanalyses were performed by Midwest Microlaboratories, Indianapolis, Ind. Aldehydes used were either reagent grade or purified by distillation or recrystallized from appropriate solvents.

N,N′-Bis(2-hydroxy-3-methoxybenzylidene)-1,3-diaminopropane (VIIa).—To a refluxing solution of 15.21 g (0.01 mole) of 2-hydroxy-3-methoxybenzaldehyde in 60 ml of absolute ethanol was added dropwise with stirring 3.71 g (0.05 mole) of 1,3-diaminopropane during a 20-min period. After the addition had been completed, the mixture wass tirred and refluxed for an additional 0.5 hr and transferred to a 125-ml erlenmeyer flask. As the mixture cooled, yellow crystals separated which were filtered and washed with ethanol to yield 17.0 g (99.3%) of desired product, mp 95–98°. Two crystallizations from ethanol afforded 16.7 g (97.5%) of long yellow needles, mp 97–98°.

Anal. Calcd for $C_{19}H_{22}N_2O_4$: N, 8.18. Found: N, 8.10.

N,N′-Bis(3,4-dimethoxybenzylidene)-1,3-diaminopropane (VIIb) was prepared in a manner similar to VIIa from 16.62 g (0.1 mole) of 3,4-dimethoxybenzaldehyde and 3.71 g (0.05 mole) of 1,3-diaminopropane providing 16.65 g (90%) of the desired di-Schiff base, mp 112–114.5°. Two recrystallization from absolute ethanol gave 16.5 g (89.2%) of colorless crystalline analytical sample, mp 114.5–115.5°.

Anal. Calcd for $C_{21}H_{26}N_2O_4$: N, 7.56. Found: N, 7.61.

N,N′-Bis(2-hydroxy-3-methoxybenzyl)-1,3-diaminopropane (VIIIa).—Using 0.1 g of PtO_2 catalyst, 6.85 g (0.02 mole) of N,N′-bis(2-hydroxy-3-methoxybenzylidene)-1,3-diaminopropane (VIIa) dissolved in 60 ml of absolute ethanol was reduced at room temperature in a low-pressure Parr hydrogenator with an initial hydrogen pressure of 3.15 kg/cm². Approximately 15 min was required to complete the reduction. The catalyst was removed by filtration and the solvent was distilled *in vacuo*. There was obtained 7.0 g (100%) of colorless solid, mp 118–120°. Recrystallization from absolute ethanol gave 6.9 g (98.6%) of pure sample, mp 119–120°.

Anal. Calcd for $C_{19}H_{26}N_2O_4$: N, 8.08. Found: N, 8.00.

N,N′-Bis(3,4-dimethoxybenzyl)-1 3-diaminopropane (VIIIb) was reduced in a manner similar to VIIb, using 0.1 g of PtO_2 and 16.65 g (0.045 mole) of VIIb in 100 ml of absolute ethanol giving 16.83 g (100%) of a light yellow oil. A 3.74-g sample of this material in 40 ml of dry ether was converted to 4.2 g (94%) of the dihydrochloride with dry HCl; mp 205-208°. Two crystallizations of this material from acetonitrile gave 4.0 g (89.5%) of an analytical sample, mp 208–209°.

Anal. Calcd for $C_{21}H_{30}N_2O_4 \cdot 2HCl$: Cl, 15.84; N, 6.26. Found: Cl, 15.84; N, 6.09.

2-Substituted 1,3-Bis(2-hydroxy-3-methoxybenzyl)hexahydropyrimidines (Table I).—The 2-substituted derivatives were prepared in the following manner. A solution of 4.92 g (0.02 mole) of *p*-[N,N-bis(2-chloroethyl)amino]benzaldehyde in 30 ml of absolute ethanol was added dropwise with stirring to a refluxing solution of 7.0 g (0.02 mole) of diamine VIIIa in 25 ml of absolute ethanol. The addition took place over a period of 0.5 hr and the mixture was refluxed for an additional 0.5 hr. The solvent was then removed *in vacuo* and the oily residue was dissolved in acetonitrile and placed in a refrigerator overnight. The crystalline solid which separated was collected and washed with acetonitrile; yield 8.0 g (80%). Two crystallizations from

TABLE V

ANTITUMOR SCREENING RESULTS FOR 1,2,3-SUBSTITUTED HEXAHYDROPYRIMIDINES

No.	Test system[a]	Dose, mg/kg	Survivors	Wt change (T − C), g	Tumor wt (T/C)[b]	% T/C[b]	ED_{50}, μg/ml	Slope
1	SA	500	6/6	−25	586/925	63		
	LL	400	7/7	−16	718/1269	56		
2	KB						13	−0.61
	SA	250	7/7	00	1174/1127	75		
	FV	200	10/10	1	1174/1127	104		
	LE	200	6/6	−6	8.7/9.2	94		
3	SA	500	4/6	−29	692/925	74		
	LL	400	5/7	−30	374/1269	27		
	LL	400	0/6					
	LE	200	6/6	−21	9.0/9.0	100		
4	KB						23	−1.01
	SA	250	7/7	−6	874/1091	80		
	FV	200	9/10	−7	1074/1127	95		
	LE	200	6/6	−2	8.3/9.2	90		
5	KB						14	−0.62
	SA	250	7/7	−8	886/1091	81		
	FV	200	10/10	−19	576/883	65		
	LE	200	6/6	−2	9.3/9.2	101		
6	KB						12	−0.63
	SA	250	6/6	−13	857/925	92		
	FV	200	10/10	−12	1113/1127	98		
	LE	200	6/6	−1	9.0/9.2	97		
7	SA	250	7/7	−13	897/1091	82		
	FV	200	10/10	9	1353/1127	120		
	LE	200	6/6	−1	8.8/9.2	95		
8	KB						8.9	−0.53
	SA	250	7/7	−23	917/1091	110		
	FV	200	10/10	−19	979/1127	86		
	LE	200	6/6	−10	10.2/9.2	110		
9	KB						4.9	−0.51
	AA	100	3/3	10				
		33	3/3	21				
		10	3/3	24				
		3	3/3	28				
	WA	50	6/6	−60	4.4/8.1	54		
11	KB						25	−1.08
	SA	500	6/6	−28	482/975	52		
		500	5/6	−21	473/591	80		
		500	1/6	−45	300/992			
	FV	400	9/10	−14	1093/953	114		
	LE	300	6/6	00	9.7/9.2	105		
12	KB						13	−0.76
	SA	500	5/6	−12	459/1392	32		
		500	6/6	−17	554/736	75		
		500	4/6	−12	590/1158	50		
	LE	350	6/6	−33	8.5/8.8	96		
13	KB						28	−1.16
	SA	250	6/6	−16	838/925	90		
	FV	200	9/10	00	1436/1127	127		
	LE	200	6/6	−9	8.2/9.2	89		
14	KB						100	
	SA	250	6/6	−7	790/512	154		
	FV	200	10/10	9	1603/1127	142		
	LE	200	6/6	10	8.5/9.2	92		
15	KB						4.7	−0.55
	SA	500	6/6	−37	393/1158	33		
		500	5/6	−34	477/736	64		
		500	5/6	−35	621/1392	44		
	LE	350	5/6	−25	8.8/8.8	100		
16	KB						5.3	−0.33
	AA	100	3/3	18				
		33	3/3	28				
		10	3/3	30				
		3	3/3	28				
	WA	50	6/6	−70	6.8/8.1	83		
17	KB						3.7	−0.47
	AA	100	3/3	7				
		33	3/3	22				

TABLE V (*Continued*)

No.	Test system[a]	Dose, mg/kg	Survivors	Wt change (T − C),[b] g	Tumor wt[c] (T/C)[b]	% T/C[b]	ED_{50}, μg/ml	Slope
17	AA	10	3/3	22				
		3	3/3	17				
	WA	50	6/6	−80	2.9/8.1	35		

[a] Screening was performed under the auspices of the Cancer Chemotherapy National Service Center according to its protocol.[6] The test systems included: WA, Walker 256 (subcutaneous) in rats, p 11 of protocol; KB, cell culture, p 22; SA, Sarcoma 180 in mice, p 5; FV, solid Friend virus leukemia, p 6; AA, toxicity test. [b] T stands for test animals, C for controls. [c] Tumor weight is in milligrams for SA, FV, and LL, and grams for WA and LE.

30-ml portions of acetonitrile provided an analytical sample, mp 103–104°.

Anal. Calcd for $C_{30}H_{37}Cl_2N_3O_4$: N, 7.31. Found: N, 7.27.

2-Substituted 1,3-Bis(3,4-dimethoxybenzyl)hexahydropyrimidines (Table II) were prepared by the procedure as described in the previous section, from aldehydes and N,N′-bis(3,4-dimethoxybenzyl)-1,3-diaminopropane (VIIIb).

Acknowledgment.—The authors acknowledge Drs. H. B. Wood and J. Leiter of the Cancer Chemotherapy National Service Center for their cooperation in making the screening data available. We also wish to thank Union Carbide Chemical Company for supplying the 1,3-diaminopropane used in this research.

3-Substituted 2-Thiohydrouracils. Synthesis and Antitubercular and Antineoplastic Activities

ARTHUR C. GLASSER AND RICHARD M. DOUGHTY

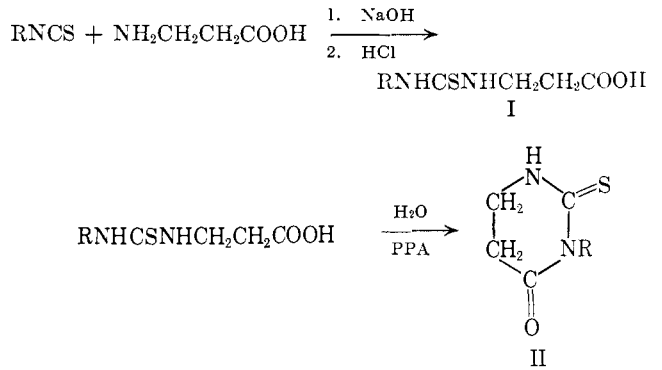
Department of Pharmaceutical Chemistry, College of Pharmacy, University of Kentucky, Lexington, Kentucky

Received August 26, 1965

A number of 3-substituted 2-thiohydrouracils were synthesized by cyclization of the appropriate 1-carboxyethyl-3-substituted 2-thioureas using polyphosphoric acid. Infrared spectral characteristics of the –NC=S containing molecules are discussed and compared. The thioureas and resulting thiohydrouracils were tested for their *in vitro* antitubercular activity with minimum inhibitory concentrations ranging from 1.3–2.5 mg % for the thioureas, and from 1.3–5.0 mg % for the thiohydrouracils. Several of the compounds were submitted to the Cancer Chemotherapy National Service Center for screening; the results of this screening are also reported.

A wide variety of chemical structures have been shown to be effective in the inhibition of the growth of *M. tuberculosis* through *in vitro* testing. These compounds range in complexity of structure from such molecules as the antibiotic streptomycin to the relatively simple substituted thiourea molecule. Numerous investigators have reported upon the synthesis and antitubercular activity of various molecules containing the elements of –NC=S such as thioamides,[1] thioureas,[2] and thiosemicarbazones.[3] Recently we have reported on the activity of some thioureas incorporating heterocyclic N-substitution along with *p*-alkoxyphenyl N-substitution.[4] The present series of compounds was synthesized and examined for the effect of incorporating –NC=S into a cyclic structure such as thiohydrouracil while maintaining certain other features such as the substituents of the previously reported series for comparison.

Chemistry.—The intermediate 1-carboxyethyl-3-substituted 2-thioureas (I) were formed in good yields by treating 3-aminopropionic acid and the appropriately substituted isothiocyanates in aqueous sodium hydroxide at room temperature and subsequent treatment with hydrochloric acid. The substituted carboxyethyl-



thioureas were then cyclized with hot polyphosphoric acid to form the 3-substituted 2-thiohydrouracils (II).

Derzaj-Bizjak and co-workers[5] reported that the condensation of 3-aminopropionic acid with isothiocyanates as reported by Ghosh[6] does not take place except in the case of *o*-tolyl isothiocyanate. These authors used the corresponding ethyl 3-aminopropionate, and, following the condensation with an isothiocyanate, the ester function was hydrolyzed to free the desired 1-carboxyethyl-3-substituted 2-thioureas. We have found that the condensation of the sodium salt of 3-aminopropionic acid with alkyl, cycloalkyl, and aryl isothiocyanates in water pro-

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