morpholine hydrochloride.[16] The allyl compound listed in Table I was obtained by the reaction of 2-dimethylaminoethyl chloride hydrochloride with allylamine using isopropyl alcohol as a solvent in the same manner described for the preparation of the diethylamino analog.[2]

2-Dimethylamino-N-methylpropionamide.—A solution of 128 g. (0.77 mole) of 2-bromo-N-methylpropionamide[17] in 200 ml. of benzene was added to a cold solution of 150 g. (3.3 mole) of dimethylamine in 700 ml. of benzene. It was necessary to cool the mixture during the initial exothermic reaction. After standing at room temperature for 3 days, the mixture was heated at 55–65° for 4 hr., cooled, and treated with a cold solution of 40 g. of sodium hydroxide in 100 ml. of water. The layers were separated and the organic phase was dried over potassium carbonate. After evaporation of the solvent, the residue was fractionated to give 77 g. (77%) of colorless product, b.p. 71–72° (2 mm.).

Anal. Calcd. for $C_6H_{14}N_2O$: N, 21.52. Found: N, 21.57.

N^1,N^2,N^2-Trimethyl-1,2-propanediamine.—A solution of 39.0 g. (0.3 mole) of the preceding amide in 50 ml. of ether was added dropwise to a suspension of 15.0 g. (0.4 mole) of lithium aluminum hydride in 600 ml. of ether and the mixture was stirred for 20 hr. at room temperature. The product (Table I) was isolated in the usual manner.[2] This diamine is apparently the major product of the reaction of $ClCH(CH_3)CH_2N(CH_3)_2 \cdot HCl$[18] and excess aqueous CH_3NH_2; b.p. 134–137°; yield 67%.[19] Samples of compound **26**, obtained from the diamine prepared by either method, had identical melting points, mixture melting points, and n.m.r. spectra.[20]

Acknowledgment.—The authors are indebted to Mr. W. A. Lott for his interest and encouragement during this investigation, to Dr. John C. Burke and his associates for the pharmacological data, and to Mr. Joseph Alicino and his associates for the analyses reported herein.

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(19) A mixture of N^1,N^1,N^2-trimethyl-1,2-propanediamine and N^1,N^2,N^2-trimethyl-1,2-propanediamine was expected from this reaction. The cyclization of $ClCH(CH_3)CH_2N(CH_3)_2$ to the ethylenimonium ion and subsequent reaction with the anion of diphenylacetonitrile yielded a mixture of isomeric products; see E. M. Schultz and J. M. Sprague, *J. Am. Chem. Soc.*, **70**, 48 (1948), and references cited therein.
(20) The authors are indebted to Dr. A. Cohen for the determination and interpretation of the n. m. r. spectra.

Synthesis of 5-Substituted Pyrimidines[1,2]

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Synthesis of a series of 5-substituted pyrimidines through the halogen–lithium exchange reaction has been reported. 2,4-Diethoxy-5-arylhydroxymethylpyrimidines prepared in this manner have been oxidized and then hydrolyzed to 5-acyluracils. The 5-acyluracils have been reduced successfully to 5-arylhydroxymethyluracils. The stability of 5-arylhydroxymethyluracils is discussed.

Many biologically active synthetic pyrimidines have been reported and most of them exert their effects on the nucleic acid metabolism of the cells.[3] The compounds reported in the literature are considered analogs of the naturally occurring pyrimidines or their nucleosides which are pyrimidines substituted with a carbohydrate moiety in the 1-position. However, more recently[4,5] a remarkably different type of nucleoside was isolated from soluble ribonucleic acid (RNA) of yeast. This is an isomer of uridine and is chemically identified as 5-ribosyluracil (pseudouridine) in which the base–ribosyl linkage is C–C instead of the usual N–C.

Little work has been done in synthesizing structural analogs of this nucleoside with potential antimetabolic activity. We wish to report here the synthesis of a series of 5-substituted pyrimidines where C-5 of the pyrimidine carries a noncarbohydrate grouping. These were prepared in order to test the dual possibility that they may be effective as (i) antimetabolites in systems where 5-ribosyluridylic acid has been implicated, as for example in the ability to incorporate C^{14}-amino acids (leucine) into RNA by certain fractions of soluble RNA which characteristically contain substantially large amounts of 5-ribosyluridylic acid,[6,7] and (ii) as antagonists of nucleic acid metabolism in bacterial and/or mammalian systems.

The method of synthesis employed here is an extension of the ones used by Langley[8] in the synthesis of 6-substituted pyrimidines and by Ulbricht[9] in the case of thymine and thymidine, where advantage is taken of the ability of pyrimidines to undergo halogen–metal interconversion reactions. Using this method Langley[8] also synthesized 2,4-dimethoxypyrimidine-5-carboxylic acid. Attention here has been focused on the reaction of 5-pyrimidinyllithium with aryl aldehydes to prepare a series of 5-substituted pyrimidines.

Our starting material, 2,4-diethoxy-5-bromopyrimidine (I), was synthesized according to the sequence of reactions reported by Hilbert and Jansen.[10] Langley's procedure[8] was adopted to synthesize the pyrimidyllithium compound (II). Reaction of II with an ether solution of an aryl aldehyde resulted in 2,4-diethoxy-5-arylhydroxymethylpyrimidine (III). These compounds were characterized by their ultraviolet and infrared absorption spectra and also elemental analysis (Table I).

The next step in the sequence was the attempted hydrolysis of the ethoxy groups of III to obtain the

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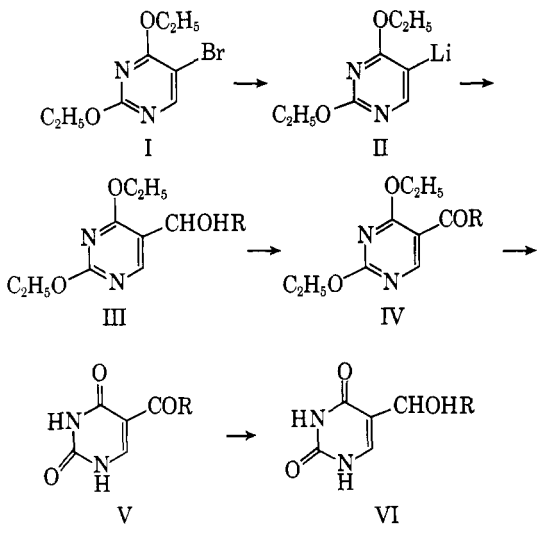

uracil derivatives (VI). However, difficulties were encountered in the reaction. Several different methods (both acid and base catalyzed) were tried in order to hydrolyze the ethoxy groups of III. None of the methods afforded a suitable approach toward the hydrolysis and isolation of the desired 5-substituted uracil derivatives (VI). In all the cases the end products were either the starting material or other ill-defined compounds which defied our attempts at characterization. All the experiments were monitored by paper chromatography and in cases where products different from the starting materials were indicated, they were isolated and elemental analysis and spectral data obtained.

The products isolated indicated a cleavage of the C–C bond at C-5 of pyrimidine. In the case of 2,4-diethoxy-5-(4-fluoro-α-hydroxybenzyl)pyrimidine, elemental analysis revealed no fluorine in the hydrolysis product, which was supporting evidence for the cleavage of the carbon–carbon linkage at C-5.

Formic acid (5, 10, 25, 50, and 90%) in sealed tubes at 150° was tried as the hydrolytic agent since Wyatt and Cohen[11] have shown that under these conditions with 88 or 98% formic acid they were able to isolate 5-hydroxymethylcytosine in good yields from phage deoxyribonucleic acid. However, this method was not adaptable in the case of the compounds reported here. Two major products, uracil and 5-benzyluracil, in approximately 20 and 65% yields, respectively, were isolated. Uracil resulted through a hydrolysis of the ethoxy groups as well as a carbon–carbon cleavage at C-5. The formation of 5-benzyluracil is possible as a result of the reduction of the benzyl alcohol derivative (III, R = phenyl) to the hydrocarbon level. This is feasible if one considers the reducing character of formic acid, especially at 150° in a sealed tube. Formic acid at refluxing temperatures in an open system was without appreciable effect either in hydrolysis or the cleavage of the carbon–carbon bond at C-5.

The difficulty encountered in hydrolysis may be due to the unexpected lability of the uracil carrying a hydroxymethyl group at C-5.[12] One of the explanations that may be given is that during hydrolysis a reversal of the synthetic pathway occurs resulting in uracil and the aldehyde. The isolation of uracil from the hydrolysate seems to support this postulation. In fact, when a 0.002 *M* solution of 5-α-hydroxybenzyluracil (prepared by an alternate procedure) in 6 *N* hydrochloric acid was heated under reflux it was converted entirely to uracil within 1 hr. The fact that C-5 of uracil (pyrimidine) is the most electrophilic center in the molecule and hence has the greatest ability to form a carbanion also explains why a uracil derivative with a hydroxymethyl group at any other position is more stable than when it is at C-5. However, evidence has been presented in the literature[13] which argues in favor of the stability of 5-hydroxymethyluracil. The ill-defined products probably arose from a cleavage and recyclization of the pyrimidine ring to a different product or from a polymerization reaction similar to that presumed to occur with 5-hydroxymethyluracil.[13]

With respect to the 6-substituted pyrimidines, Langley[8] observed that acid hydrolysis of 2,4-diethoxy-6-alkylhydroxymethyl pyrimidines to the corresponding 6-substituted uracils resulted in their conversion to the imidazolones through the opening of the pyrimidine ring and recyclization. Here, the carbon–carbon bond at C-6 was not cleaved. 2,4-Diethoxy-6-phenylhydroxymethyl pyrimidine was, however, successfully hydrolyzed with acid to the uracil derivative without ring opening or cleavage of the carbon–carbon bond at C-6.

The difficulty in hydrolysis was overcome by oxidation of III to 2,4-diethoxy-5-acylpyrimidine (IV). Two methods of oxidation were tried. One of them entailed oxidation with alkaline potassium permanganate. Here, the product isolated was 5-benzoyl-4-ethoxy-2-pyrimidinol which on acid hydrolysis yielded 5-benzoyluracil (V, R = phenyl). 5-Benzoyl-4-ethoxy-2-pyrimidinol was identified through the bathochromic shift in its ultraviolet absorption maximum with a change in pH and also elemental analysis. This method of oxidation, however, was not reproducible and also failed to give clean products in satisfactory yields.

In the second method, chromium trioxide–pyridine complex was employed as the oxidizing agent.[14] This method proved to be very effective and the oxidation products (IV) were characterized through their ability to form analytically pure oximes, and also by means of elemental analysis and ultraviolet and infrared absorption spectra. The ultraviolet spectra exhibited a high extinction coefficient indicative of a conjugated carbonyl group (Table II).

The hydrolysis of IV to 5-acyluracils (V) was easily accomplished by heating for 20–30 min. in the presence of 6 *N* hydrochloric acid. This also points out the ease of hydrolysis without a carbon–carbon cleavage at C-5, when that position is substituted by a group other than a hydroxymethyl. The 5-acyluracils also formed oximes. Their ultraviolet absorption spectra exhibited a bathochromic shift with a change in pH characteristic of a uracil moiety devoid of the ethoxy groups (Table II).

The reduction of the 5-acyluracils (V) to 5-arylhydroxymethyluracils (VI) was achieved by the use of potassium borohydride in aqueous solution. A sig-

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TABLE I

RCHOHR′

Compound no.	R	R′	B.p., °C. (mm.) or m.p., °C.	R_f	Yield, %	λ_{max} mμ	ϵ_{max}
III	2,4-Diethoxy-5-pyrimidinyl	Phenyl	140–160 (0.08)	0.93	70	266[a]	6175
VII	2,4-Diethoxy-5-pyrimidinyl	4-Fluorophenyl	87–88 (0.4)	.93	27	273[a]	5220
VIII	2,4-Diethoxy-5-pyrimidinyl	*p*-Tolyl	100–105 (0.3)	.93	46	266[a]	5070
IX	2,4-Diethoxy-5-pyrimidinyl	Furfuryl	110–112	.93	40	266[a]	7092
VI	2,4-Dihydroxy-5-pyrimidinyl	Phenyl	221–223	.59	40	265[b]	7624
						288[c]	6235
X	2,4-Dihydroxy-5-pyrimidinyl	4-Fluorophenyl	325–328 dec.	.70	45	265[b]	6353
						288[c]	5580
XI	2,4-Dihydroxy-5-pyrimidinyl	*p*-Tolyl	316–317 dec.	.69	45	263[b]	6892
						288[c]	5681

[a] Spectra measured in ethanol. [b] Spectra measured in 0.1 *N* HCl. [c] Spectra measured in 0.1 *N* NaOH.

TABLE II

R—C(=O)—R′

Compound no.	R	R′	B.p., °C. (mm.) or m.p., °C.	R_f	Yield, %	λ_{max}	ϵ_{max}
IV	2,4-Diethoxy-5-pyrimidinyl	Phenyl	150–160 (0.1)	0.90	60	252[a,b]	14,480
						273–275[b]	
XII	2,4-Diethoxy-5-pyrimidinyl	4-Fluorophenyl	93–95	.91	52	254[a,b]	14,844
						270–272[b]	
XIII	2,4-Diethoxy-5-pyrimidinyl	*p*-Tolyl	110–130 (0.05)	.90	69	270[b]	16,975
V	2,4-Dihydroxy-5-pyrimidinyl	Phenyl	296–298 dec.	.49	44	252[a,c]	
						279[c]	13,792
						252[d]	11,104
						309[d]	14,368
XIV	2,4-Dihydroxy-5-pyrimidinyl	4-Fluorophenyl	281–283 dec.	.59	67	252[a,c]	
						279[c]	19,219
						252[d]	10,242
						309[d]	11,860
XV	2,4-Dihydroxy-5-pyrimidinyl	*p*-Tolyl	298–299 dec.	.60	68	280[c]	16,717
						260[d]	13,014
						310[d]	13,873
XVI	4-Ethoxy-2-hydroxy-5-pyrimidinyl	Phenyl	186–187	.72	12	276[c]	15,296
						256[d]	10,890
						302[d]	17,568

[a] Appears as a shoulder. [b] Spectra measured in alcohol. [c] Spectra measured in 0.1 *N* HCl. [d] Spectra measured in 0.1 *N* NaOH.

nificant drop in the molar extinction coefficients of the reduced compounds was observed and the values corresponded to those normally observed for pyrimidines without a conjugated carbonyl group (Table I). The infrared absorption spectra exhibited a band indicative of a hydroxyl group (3600 cm.$^{-1}$).

In a preliminary report, Ulbricht[15] has reacted 5-pyrimidyl-lithio compounds with aldehydosugars to yield 5-substituted nucleosides. It is possible that much better yields of these compounds can be obtained by use of benzyl ethers of uracil which can be removed by hydrogenation rather than acid hydrolysis.

Experimental

Melting points are corrected and were determined on a Mel-Temp unit made by Laboratory Devices. All ultraviolet spectra were taken on a Beckman DU or a Zeiss spectrophotometer. The infrared spectra were run as KBr pellets or as Nujol mulls on a Perkin–Elmer Infracord spectrophotometer. Ether and tetrahydrofuran used in the reactions were distilled from lithium aluminum hydride and stored over sodium wire. All experiments with organolithium compounds were carried out in an atmosphere of dry oxygen-free nitrogen; magnetic stirring was employed in all cases. *n*-Butyllithium was either prepared by the method of Gilman[16] starting from *n*-butyl bromide which was dried over phosphorus pentoxide, decanted, and distilled, or was purchased from the Lithium Corporation of America as a heptane solution. It was estimated by differential titration.[17]

2,4-Diethoxy-5-arylhydroxymethylpyrimidine (III, R = C_6H_5).—In a 300 ml. three-necked flask equipped with a dropping funnel, a nitrogen inlet tube, a condenser, and a low temperature thermometer (the latter was suspended in the condenser) was placed 2,4-diethoxy-5-bromopyrimidine (I) (4.94 g., 20 mmoles) in about 100 ml. of dry tetrahydrofuran. The flask was cooled to about −70° in a Dry Ice–acetone bath and *n*-butyllithium (pre-cooled to −70° (2.0 *M*, 10.5 ml., 21 mmoles) was added dropwise with stirring to obtain an orange colored solution. After stirring for about 5 min., a solution of benzaldehyde (or other aldehyde) (2.12 g., 20 mmoles) in 30 ml. dry ether, was added over a period of 5 min. The contents of the flask were stirred for about 1 hr. at −70° and then the cooling bath was removed, allowing the reaction mixture to warm to about 20°. Approximately 30 ml. of 2 *N* sulfuric acid was added with stirring and the organic layer was separated. The aqueous layer was extracted with ether and the combined ether extracts were washed with water and dried over anhydrous sodium sulfate. Ether was removed by evaporation *in vacuo* and the residue was sublimed. The fraction subliming between the temperatures of 140 and 160° (0.08 mm.) was collected to obtain 3.9 g. (70%) of a pale yellow sirup which solidified to a semisolid when allowed to stand at 5° for a few weeks; R_f 0.93.

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		Carbon, %		Hydrogen, %		Nitrogen, %		Fluorine, %	
λ_{min}	ϵ_{min}	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
245	2766	65.67	65.79	6.61	6.86	10.21	10.25		
248	2102	61.63	61.82	5.86	5.43	9.58	9.39	6.50	6.30
250	3367	66.64	66.84	6.99	7.13	9.71	9.60		
247	4006	59.09	50.04	6.06	6.13	10.60	10.69		
235		60.54	60.79	4.63	4.84	12.84	12.78		
249									
235	2165	55.93	55.92	3.81	3.90	11.86	11.86	8.05	8.27
250	3012								
237	2824	62.07	61.85	5.17	5.38	12.07	11.98		
250	2987								

		Carbon, %		Hydrogen, %		Nitrogen, %		Fluorine, %		M.p. of	Nitrogen, % (oxime)	
λ_{min}, mμ	ϵ_{min}	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	oxime, °C.	Calcd.	Found
230	5600	66.17	66.10	5.88	6.10	10.29	10.21			122–125	14.63	15.37
231	5413	62.07	61.99	5.17	5.33	9.65	9.79	6.55	6.71	146–148	13.77	14.04
233	4373	67.13	67.16	6.29	6.51	9.79	9.58			150–152	13.95	14.10
		61.11	60.91	3.70	3.53	12.96	13.06			233–235 dec.	18.18	17.95
225												
236												
279												
		56.41	56.42	2.99	3.16	11.96	12.11	8.12	7.84	242–243 dec.	16.87	16.81
227	5856											
236	8892											
279	5679											
227	6574	62.61	62.58	4.35	4.52	12.17	12.45			245–247 dec.	17.14	16.98
238	9379											
283	8482											
227		63.93	63.96	4.92	4.99	11.47	11.38					
238												
277												

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.79; H, 6.86; N, 10.25. The ultraviolet absorption spectra in ethanol showed λ_{max} 266 mμ (ϵ 6175) and λ_{min} 245 mμ (ϵ 2766).

Exactly the same procedure was followed for the preparation of compounds VII, VIII, and IX.

5-Benzoyl-4-ethoxy-2-pyrimidinol (XVI).—2,4-Diethoxy-5-α-hydroxybenzylpyrimidine (III) (0.2 g., 0.73 mmole) was dissolved in 2 ml. of 10% sodium hydroxide. Potassium permanganate (0.8 g.) in 50 ml. of water was added to this and the mixture heated under reflux while stirring until the pink color was discharged. This required approximately 1.5 hr. The flask was cooled, acidified with 2 *N* sulfuric acid, and the dark-colored manganese dioxide decolorized by the addition of 10% sodium bisulfite. The mixture was concentrated by evaporation *in vacuo* and the product was recrystallized from an ethanol–water mixture, yielding 21 mg. (12%) of a white solid, m.p. 186–187°; R_f 0.72.

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.92; N, 11.47. Found: C, 63.96; H, 4.99; N, 11.38. Ultraviolet absorption: λ_{max} 276 mμ (ϵ 15,295), λ_{min} 227 mμ (0.1 *N* HCl). λ_{max} 256 mμ (ϵ 10,890) and 302 mμ (ϵ 17,568), λ_{min} 238 mμ and 277 mμ (0.1 *N* NaOH).

2,4-Diethoxy-5-benzoylpyrimidine (IV).—A solution of 2,4-diethoxy-5-α-hydroxybenzylpyrimidine (III), (2.74 g., 10 mmoles) in pyridine (30 ml.) was added slowly with stirring to the complex formed from chromium trioxide (3.0 g.) and pyridine (30 ml.), maintaining the temperature between 10 and 20°. The dark brown mixture was allowed to stand at room temperature overnight and then was poured into water (500 ml.). The water layer was extracted with five 120-ml. portions of ether. The ether extract was washed successively with three 50-ml. portions of water, three 50-ml. portions of 3 *N* hydrochloric acid, and three 40-ml. portions of water and dried over anhydrous sodium sulfate. Ether was removed *in vacuo* and the residue was sublimed to yield 1.62 g. (60%) of a sirup, b.p. 150°–160° (0.1 mm.); R_f 0.90.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.17; H, 5.88; N, 10.29. Found: C, 66.10; H, 6.10; N, 10.21. Ultraviolet absorption λ_{max} 252 mμ (ϵ 14,480), a shoulder at 273–275 mμ (ϵ 12,000), and λ_{min} 230 mμ (ϵ 5600) in ethanol.

Similar procedure was adopted for the synthesis of compounds XII and XIII.

The oxime was prepared by heating the ketone in alcohol under reflux with hydroxylamine hydrochloride in pyridine; m.p. 122–125°.

Anal. Calcd. for $C_{15}H_{16}N_3O_3$: N, 14.63. Found: N, 15.37.

5-Benzoyluracil (V).—2,4-Diethoxy-5-benzoylpyrimidine (IV) (0.26 g., 1 mmole) was heated under reflux with 6 *N* hydrochloric acid (2 ml.) for 30 min. A solid separated and was recrystallized from ethanol–water mixture; yield 0.072 g. (35%), m.p. 296–298° dec., R_f 0.49.

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.70; N, 12.96. Found: C, 60.91; H, 3.53; N, 13.06. Ultraviolet absorption: λ_{max} 279 mμ (ϵ 13,793), λ_{min} 225 mμ (0.1 *N* HCl). λ_{max} 252 mμ (ϵ 11,104) and 309 mμ (ϵ 14,368), λ_{min} 236 mμ 279 mμ (0.1 *N* NaOH). An analogous procedure was employed for synthesizing compounds XIV and XV.

The ketone yielded an oxime, m.p. 233–235° dec.

Anal. Calcd. for $C_{11}H_9N_3O_3$: N, 18.18. Found: N, 17.95.

5-α-Hydroxybenzyluracil (VI).—5-Benzoyluracil (V) (0.075 g., 0.25 mole) was added to a solution of potassium borohydride (0.037 g.) in 2 ml. of water. The mixture was stirred vigorously for about 10 min. at room temperature and then for a further 5 min. at 100°. On acidifying with 3 *N* hydrochloric acid and cooling in ice there was obtained 0.03 g. (40%) of a white solid. It was recrystallized from ethanol, m.p. 221–223°, R_f 0.59.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.63; N, 12.84. Found: C, 60.79; H, 4.84; N, 12.78. Ultraviolet absorption: λ_{max} 265 mμ (ε 7624), λ_{min} 235 mμ (0.1 *N* HCl). λ_{max} 288 mμ (ε 6235), λ_{min} 250 mμ (0.1 *N* NaOH). Compounds X and XI were synthesized in the same manner.

Paper Chromatography.—The pyrimidines reported here were chromatographed on Whatman No. 1 paper by the descending technique in the butanol–water (86:14 v./v.) solvent system of Markham and Smith.[18] The chromatogram was run 18–20 hr. at room temperature and air dried, and the spots were located by means of a Mineralight ultraviolet lamp.

Biological Data.—Compounds V and VI along with 5-benzyluracil and 5-hydroxymethyluracil were tested against a wild strain and also a uracil-requiring mutant of *Escherichia coli* at a final concentration of 25 and 100 γ/ml. During the course of an 8 hr. period both the control and the analog containing cultures showed the same rate of growth, indicating no inhibition of growth by these analogs. With the uracil-requiring mutant of *E. coli* the experiments were carried out under growth-limiting concentrations of uracil (1.0 ml). All the compounds reported here have been submitted to the National Cancer Testing Service to test for antitumor activity.

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Thyromimetics. I. The Synthesis and Hypocholesteremic Activity of Some 3′ and 3′,5′-Alkyl and Aryl-3,5-diiodothyronines

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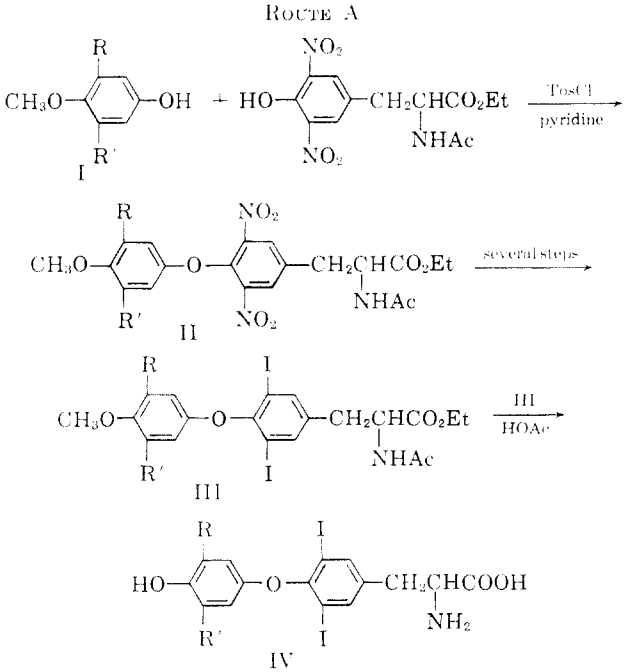
The syntheses of a number of alkyl and aryl derivatives of 3,5-diiodothyronine are described. Diphenyl ether intermediates required for these syntheses were prepared by one of two general procedures. The ability of the final compounds (IVa–h and XIa, d) to lower plasma cholesterol levels in rats fed a cholesterol–cholic acid diet is also reported.

The possibility that high serum cholesterol levels may in some way be involved in the etiology of atherosclerosis has led many investigators to study agents which cause a decrease in serum cholesterol. Thyromimetic compounds, as a class, have been among the most intensively studied of these agents.

Therefore, a number of compounds related to thyroxine and triiodothyronine had been prepared in our laboratories as part of a continuing program of chemical synthesis to provide compounds for biological evaluation as potential hypocholesteremic agents.[1–3] However, in light of the current interest in thyroxine-like compounds having alkyl groups, usually methyl groups, in place of iodine atoms[4–13] it seemed of interest to extend this approach and to prepare other alkyl derivatives of thyroxine and triiodothyronine. The studies of Jorgensen and his coworkers[6–8,12–14] in trying to determine what structural features are important for thyromimetic activity led us to prepare a series of 3′ and 3′,5′-alkyl and aryl-3,5-diiodothyronines for testing as cholesterol-lowering agents.

The compounds were prepared by two general routes. The first of these (route A) followed closely the method of synthesis developed by Chalmers, *et al.*,[15] for the preparation of thyroxine.

ROUTE A



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