After the addition of ice water, the precipitate was filtered and recrystallized from water; m.p. > 340°; yield 0.1 g. (7%).

Anal. Calcd. for $C_5H_6O_2N_4S$: C, 32.92; H, 3.31; N, 30.75. Found: C, 32.50; H, 3.27; N, 30.40.

7-Methyl-6-thia-2-keto-1,2,3,6-tetrahydropurine-6,6-dioxide (IXa, Table IV). To a stirred solution of 8.8 g. of 1-methyl-4-amino-5-sulfamylimidazole (VII, 25) in 150 ml. of 4% aqueous sodium hydroxide there was added, dropwise, 70 ml. of 12.5% phosgene in benzene. Near the end of the addition, a solid began to separate and very small portions of 25% aqueous sodium hydroxide were added to dissolve the solid. The mixture was stirred for 4 hr., cooled, and made strongly acidic with concentrated hydrochloric acid. The precipitate was filtered, m.p. 225–227° dec.; yield 6.4 g. The filtrate, after the addition of more hydrochloric acid, was kept in a refrigerator whereupon an additional 2.3 g. of product precipitated, m.p. 226–228° dec.; total yield 8.7 g. (86%).

7-Methyl-6-thia-2-thioketo-1,2,3,6-tetrahydropurine-6,6-dioxide (IXb, Table IV). Thiophosgene (2.3 g.) was added to a stirred solution of 3.5 g. of 1-methyl-4-amino-5-sulfamylimidazole (VII, 25) in 46 ml. of 4% aqueous sodium hydroxide, cooled in an ice bath. The mixture was stirred for 4 hr. at room temperature. The precipitate was filtered (A) and washed with a small amount of 2*N* hydrochloric acid.

The filtrate (A) was cooled in an ice bath and made strongly acidic with concentrated hydrochloric acid; an additional amount of product precipitated.

1,3,7-Trimethyl- (X) *and 3,7-dimethyl-6-thia-2-keto-1,2,3,6-tetrahydropurine-6,6-dioxide* (XI, Table IV). To a stirred solution of 3 g. of 7-methyl-6-thia-2-keto-1,2,3,6-tetrahydropurine-6,6-dioxide (IXa) in 45 ml. of 5% aqueous sodium carbonate there was added 5.6 g. of methyl sulfate. After 1 hr., a solid began to separate and a small amount of saturated aqueous sodium carbonate solution was added to dissolve the solid. The mixture was stirred for 12 hr. and cooled in an ice bath for several hours. The precipitate (X) was filtered.

The filtrate was acidified with concentrated hydrochloric acid and kept in a refrigerator for 12 hr. The precipitate (XI) was filtered.

1,7-Dimethyl-6-thia-2-keto-1,2,3,6-tetrahydropurine-6,6-dioxide (XIIIa, Table IV). Phosgene (14 ml. of 12.5% phosgene in benzene) was added, dropwise, to a stirred solution of 1.9 g. of 1-methyl-4-amino-5-(methylsulfamyl)imidazole (XII, 33) in 25 ml. of 4% aqueous sodium hydroxide. A few drops of 25% aqueous sodium hydroxide solution were added, if necessary, to dissolve any precipitated solid. After 3 hr., the aqueous layer was separated, cooled, and made strongly acidic with concentrated hydrochloric acid. The precipitate was filtered.

1,7-Dimethyl-6-thia-2-thioketo-1,2,3,6-tetrahydropurine-6,6-dioxide (XIIIb, Table IV). To a stirred solution of 3.8 g. of 1-methyl-4-amino-5-(methylsulfamyl)imidazole (XII, 33) in 36 ml. of 4% aqueous sodium hydroxide solution, cooled in an ice bath, there was added 2.3 g. of thiophosgene. The mixture was stirred for 4 hr. at room temperature and the product was filtered.

ANN ARBOR, MICH.

[CONTRIBUTION FROM COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

1-Alkoxy-4-phenyl-4-propionoxypiperidines and Their 3-Methyl Homologs* as New Analgesics

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α- and β-1-alkoxy-3-methyl-4-phenyl-4-propionoxypiperidines have been made and examined for analgesic action in rats. The β-isomers are much more active than the α-isomers. Several related compounds have been prepared. It was found that heating the 1-alkoxy-4-phenyl-4-hydroxypiperidines or their 3-methyl homologs with propionic anhydride did not result in acylation of the hydroxy group but in elimination of the 1-alkoxy group with formation of the *N*-acylated piperidine. A mechanism for this reaction is offered. The α- and β-1-alkoxy-3-methyl-4-phenyl-4-propionoxypiperidines were related stereochemically to the corresponding amines, alphaprodine and betaprodine.

Lee and his co workers[1] first prepared a series of 1-alkyl-3-methyl-4-aryl-4-propionoxypiperidine hydrochlorides some of which have strong analgesic action. One of this series, alphaprodine hydrochloride, 1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride, has found wide use as an analgesic in human medicine.[2]

In view of the similarities between the biological activities of some alkoxyamines and those of the related alkylamines[3] it was decided to synthesize some analogous compounds by replacing the *N*-alkyl group in the prodines of Lee with an *N*-alkoxy group.

The methods employed in the synthesis of the 1-alkoxy-4-phenyl-4-propionoxypiperidines and their 3-methyl homologs were similar to those used by Lee and co-workers[1] and are shown in Scheme A.

The required β-alkoxyamino esters, *N*-alkoxy-*N*-β-carbomethoxyethylamine (I), *N*-alkoxy-*N*-β-carbomethoxypropylamine (II), and *N*-alkoxy-*N*,*N*-bis(β-carbomethoxyethyl)amine (III) were prepared by the addition of alkoxyamines in methanol to methyl acrylate or methyl methacrylate, respectively. However, it was found that this reaction proceeds much slower than that described for

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* Kindly supplied by Dr. J. Lee, Hoffmann-La Roche Inc., Nutley, N. J.

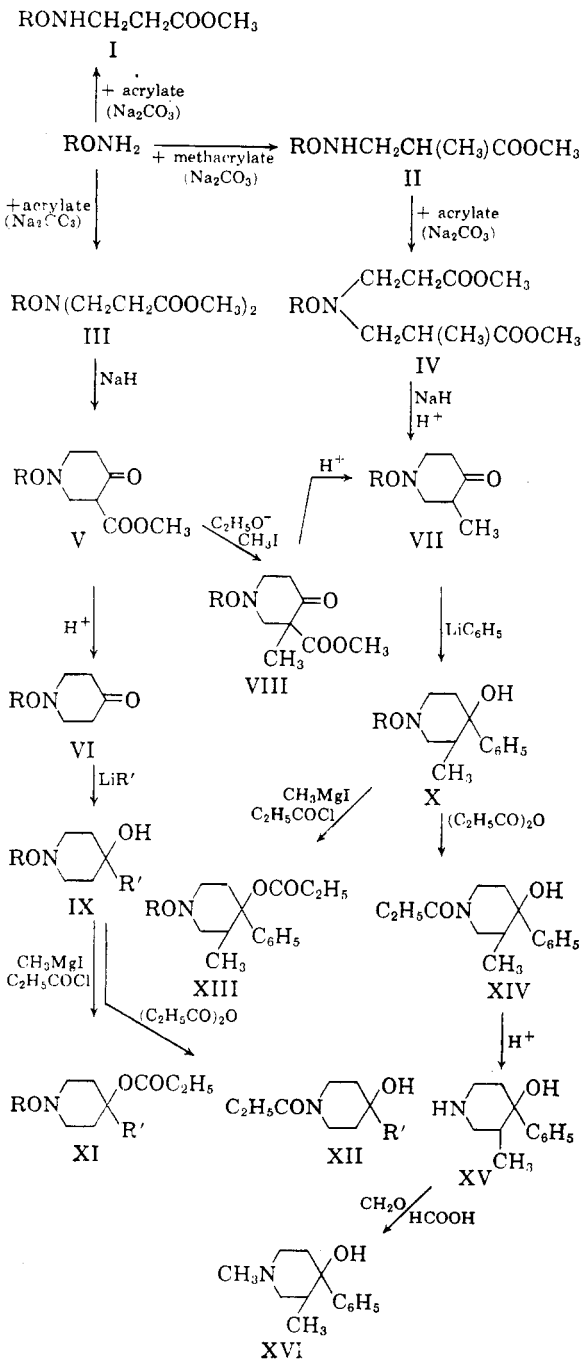
(1)(a) A. Ziering, L. Berger, S. D. Heinemann, and J. Lee, *J. Org. Chem.*, 12, 894 (1947); (b) L. Berger, A. Ziering, and J. Lee, *J. Org. Chem.*, 12, 904 (1947); (c) A. Ziering, and J. Lee, *J. Org. Chem.*, 12, 911 (1947); (d) A. Ziering, A. Motchane, and J. Lee, *J. Org. Chem.*, 22, 152 (1957).

(2) American Medical Association Council on Drugs, *New and Nonofficial Drugs*, J. B. Lippincott Co., Philadelphia, 1959, p. 313.

(3) L. W. Jones and R. T. Major, *J. Am. Chem. Soc.*, 49, 1527 (1927).

the more basic, corresponding alkylamines.[4,5] Methyl acrylate furnished mainly the secondary amine, I, and methyl methacrylate gave only traces of II. Moreover, these results proved to be unreproducible. Eventually, anhydrous sodium carbonate was found to be a good catalyst; consistently high yields of the amines, III, and fair yields of the amines, II, could be obtained in its presence. The tertiary amine, *N*-alkoxy-*N*-β-carbomethoxyethyl - *N* - β - carbomethoxypropylamine (IV) was prepared in the same way in excellent yields by addition of II to methyl acrylate.

Scheme A



The bisesters, III and IV, could be cyclized easily in a Dieckmann condensation with sodium hydride as the condensing agent.[4] The intermediate β-keto esters, 1-alkoxy-3-carbomethoxy-4-piperidones (V) and 1-alkoxy-3-methyl-3-carbomethoxy-4-piperidones (VIII), were either isolated or hydrolyzed and decarboxylated without isolation to give 1-alkoxy-4-piperidones (VI) or 1-alkoxy-3-methyl-4-piperidones (VII), respectively.

The piperidones, VII, were prepared by methylation of the β-keto esters, V, and subsequent saponification and decarboxylation.[5,6] The time consuming preparation of the amino esters, II and IV may be circumvented in this way.

The 4-piperidones VI and VII reacted with phenyllithium or butyllithium in the expected way to furnish the carbinols, 1-alkoxy-4-phenyl(or butyl)-4-hydroxypiperidines (IX) or 1-alkoxy-3-methyl-4-phenyl-4-hydroxypiperidines (X). The diastereomers of the latter could be separated by fractional crystallization of the hydrochlorides from acetone and of the free bases from ligroin. The less soluble bases which formed the more soluble hydrochlorides were named the α-isomers and the more soluble bases with the less soluble hydrochlorides the β-isomers since the former could be converted into α-1,3-dimethyl-4-phenyl-4-hydroxypiperidine[1c] (alphaprodine alcohol XVI) by procedures described below which should not have changed the stereochemical nature of the molecule.

The acylation of the tertiary alcohols IX and X proceeded only with difficulty. Only starting material could be recovered after prolonged heating with propionyl chloride in pyridine. The original method of Lee[1] produced unexpected results which will be discussed below. Eventually, a good way for the acylation was found to be the conversion of the carbinols into alcoholates by means of methyllithium or better methylmagnesium iodide and subsequent addition of propionyl chloride. High yields of the desired esters, 1-alkoxy-4-phenyl-(or butyl)-4-propionoxypiperidine (XI) and 1-alkoxy-3-methyl-4-phenyl-4-propionoxypiperidine (XIII), were obtained in a smooth reaction. Propionic anhydride gave in this process only mixtures of these esters with unchanged carbinol which were not easily separated. The esters XI and XIII were usually not isolated as such but were purified as the readily crystallizable hydrochlorides.

Lee and associates[1] converted 1-methyl-4-phenyl-4-hydroxypiperidine and the isomers of the 1,3-dimethyl-4-phenyl-4-hydroxypiperidines (XVI) into the corresponding propionates by prolonged

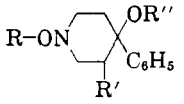
(4) S. M. McElvain and K. Rory, *J. Am. Chem. Soc.*, **70**, 1820, 1826 (1948).

(5) D. R. Howton, *J. Org. Chem.*, **10**, 277 (1945).

(6) G. R. Clemo and T. P. Metcalfe, *J. Chem. Soc.*, 1518 (1937).

TABLE I

PHARMACOLOGICAL TESTS OF *N*-ALKOXYPIPERIDINES



R	R′	R″	Isomer	LD_{50}[a]	Dose, Mg./Kg.	Analgetic Activity[b]	Side Reactions
CH_3	H	C_2H_5CO	—	197	192 s.c.	None	Mild depression
					320 Oral	None	Mild depression
CH_3	CH_3	H	α	520	256 s.c.	None	Slight depression
					320 Oral	None	Slight depression
CH_3	CH_3	H	β	98	128 s.c.	None	Very toxic
					320 Oral	None	Very toxic
C_2H_5	CH_3	H	α	686	256 s.c.	None	Slight depression
C_2H_5	CH_3	H	β	86	128 s.c.	None	None
					320 Oral	None	Very toxic
CH_3	CH_3	C_2H_5CO	α	343	128 s.c.	None	Tenseness
					320 Oral	None	None
CH_3	CH_3	C_2H_5CO	β	171	93 s.c.	Marked, about 2 hr. duration	Tenseness
					93 Oral[c]	Strong, equal to 100–150 mg. of Demerol	Depression, later excitement, signs of toxicity
					155 Oral	Strong	Very toxic
C_2H_5	CH_3	C_2H_5CO	α	520	77 s.c.	Trace	None
					256 Oral[c]	Trace	None
C_2H_5	CH_3	C_2H_5CO	β	394	56 s.c.	None	None
					56 Oral	Moderate, Equal to about 50 mg. of Demerol	Depression and hypnosis
					280 Oral	Very strong	Very toxic

[a] Mg./kg. intraperitoneal in mice. [b] In rats. [c] It is of interest to note that these compounds showed better oral than subcutaneous activity.

heating with an excess of propionic anhydride with or without catalyst. The same procedure was applied to the carbinols (IX. R = CH_3,C_2H_5; R′ = C_6H_5) and a neutral compound was obtained in addition to the desired esters, XI. Both the 1-methoxycarbinol and the 1-ethoxycarbinol gave the same product which indicated that the alkoxy group had been removed. The compound was found to be 1-propionyl-4-phenyl-4-hydroxypiperidine (XII) by means of the elementary analysis, the infrared spectrum and the lack of basicity.

Both the α-1-methoxy- and the α-1-ethoxy-3-methyl-4-phenyl-4-hydroxypiperidine (X, R = CH_3,C_2H_5) were submitted to the same procedure. None of the desired esters, XIII, could be isolated but the cleavage of the *N*-alkoxy groups furnished 1-propionyl-3-methyl-4-phenyl-4-hydroxypiperidine (XIV). The structure of this amide and its stereochemical relation to the α-1,3-dimethyl-4-phenyl-4-hydroxypiperidine (XVI) of Ziering and Lee[1c] was confirmed as follows.

Hydrolysis of the amide, XIV, with dilute alkali furnished α-3-methyl-4-phenyl-4-hydroxypiperidine (XV). The latter could be methylated quantitatively by the Eschweiler-Clarke method[7] to give α-1,3-dimethyl-4-phenyl-4-hydroxypiperdine (XVI). This compound was found identical in every respect with an authentic sample* prepared by Ziering and Lee.[1c]

A clue as to the way in which the cleavage of the *N*-alkoxy group of the 1-alkoxy-4-phenyl-4-hydroxypiperidines (IX) and their 3-methyl homologues (X) occurred upon heating with propionic anhydride was provided by the distinct aldehyde odor which was noticed during the reaction. No attempts have been made to isolate this aldehyde but there seem to be some similarities between this reaction and reactions reported in the literature. Meisenheimer[8] described the thermal decomposition of *N*-alkoxytrimethylammonium hydroxides into trimethylamine, aldehyde, and water.

It is possible that the newly found reaction takes place in two steps. The initial reaction might consist of an attack of an acylium cation on the nitrogen[9] followed by elimination of the aldehyde. However, the reaction has not been studied sufficiently to be sure of the mechanism.

The stereochemistry of alphaprodine (the propionate ester of XVI) has been discussed recently by

(7) M. L. Moore, *Org. Reactions*, 301 (1949).

* Kindly supplied by Dr. J. Lee, Hoffmann-La Roche, Inc., Nutley, N. J.

(8) J. Meisenheimer, *Ann.*, **397**, 273 (1913).

(9) V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1409 (1953).

TABLE II

REACTION PRODUCTS OF ALKOXYAMINES WITH METHYL ACRYLATE AND METHYL METHACRYLATE

$RON(R')CH_2CH(R'')COOCH_3$

R	R′	R″	Formula	B.P./Mm.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	H	H	$C_6H_{11}NO_3$	70°/14	45.10	8.33	10.52	45.19	8.42	10.46
C_2H_5	H	H	$C_7H_{13}NO_3$	87°/18	48.96	8.90	9.52	48.75	8.99	9.32
CH_3	H	CH_3	$C_7H_{13}NO_3$	68°/ 8	48.96	8.90	9.52	49.11	9.01	9.28
C_2H_5	H	CH_3	$C_7H_{15}NO_3$	78°/12	52.15	9.38	8.69	52.50	9.38	8.44
CH_3	$CH_2CH_2COOCH_3$	H	$C_9H_{17}NO_5$	139°/14	49.30	7.82	6.39	49.47	7.81	6.43
C_2H_5	$CH_2CH_2COOCH_3$	H	$C_{10}H_{19}NO_5$	138°/12	51.49	8.21	6.01	51.36	8.05	5.88
CH_3	$CH_2CH_2COOCH_3$	CH_3	$C_{10}H_{19}NO_5$	134°/12	51.49	8.21	6.01	51.60	8.14	6.20
C_2H_5	$CH_2CH_2COOCH_3$	CH_3	$C_{11}H_{19}NO_5$	137°/14	53.42	8.56	5.66	53.38	8.55	5.94

Beckett, Cary, and Kirk[10a] as well as by Ahmed, Barnes, and Kartha.[10b]

We are indebted to Dr. P. D. Orahovats and Mr. C. A. Ross of the Merck Institute of Therapeutic Research in Rahway, N. J., for a report on the analgesic action of some of the new compounds; it is compiled in Table I.

EXPERIMENTAL

Melting points and boiling points are uncorrected.

N-Alkoxy-N-β-carbomethoxyethylamines (I) *and N-alkoxy-N,N-bis(β-carbomethoxyethyl(amines* (III). *Preparation without catalyst.* A mixture of 45.5 g. (0.75 mole) of ethoxyamine, 206 g. (2.40 mole) of methyl acrylate, and 100 ml. of methanol was refluxed for 8 hr. The excess of acrylate was distilled at atmospheric pressure. The residue furnished upon distillation over a 15-cm. Vigreux column 77 g. (70%) of *N*-ethoxy-*N*-β-carbomethoxyethylamine, b.p. 87°/18 mm., and 26 g. (15%) of *N*-ethoxy-*N,N*-bis(β-carbomethoxyethyl)-amine, b.p. 138°/12 mm. The analytical data are recorded in Table II.

Preparation with catalyst. A mixture of 137 g. (2.25 moles) of ethoxyamine, 775 g. (9.00 moles) of methyl acrylate, 300 ml. of methanol, and 2 g. of powdered anhydrous sodium carbonate was refluxed with stirring for 20 hr. Distillation of the mixture afforded 460 g. (88%) of *N*-ethoxybis(β-carbomethoxyethyl)amine, b.p. 138°/12 mm. The corresponding *N*-methoxy compounds were prepared in the same way; the yields were without catalyst 30% of secondary amine and 50% of tertiary amine and with catalyst 90% of tertiary amine.

N-Alkoxy-N-β-carbomethoxypropylamines (II) *and N-alkoxy-N-β-carbomethoxyethyl-N-β-carbomethoxypropylamines* (IV). A mixture of 30.5 g. (0.65 mole) of methoxyamine, 165 ml. (1.56 moles) of methyl methacrylate, 50 ml. of methanol, and 2 g. of anhydrous sodium carbonate was refluxed with stirring for 7 days. Most of the excessive starting materials was distilled at atmospheric pressure. The residue consisted partly of polymerized methacrylate. It was distilled *in vacuo*. Eventually, all the polymer depolymerized; the yellow distillate furnished upon redistillation over a short Vigreux column 41 g. (43%) of *N*-methoxy-*N*-β-carbomethoxypropylamine, b.p. 68°/8 mm. No tertiary amine could be detected.

The corresponding *N*-ethoxy compound was prepared in the same way in 15% yield.

A mixture of 62 g. (0.42 mole) of *N*-methoxy-*N*-β-carbomethoxypropylamine (II), 146 g. (1.68 moles) of methyl acrylate, 50 ml. of methanol, and 2 g. of anhydrous sodium carbonate was refluxed for 2 days. Distillation of the product furnished 90 g. (92%) of *N*-methoxy-*N*-β-carbomethoxyethyl-*N*-β-carbomethoxypropylamine (IV), b.p. 134°/12 mm.

The corresponding *N*-ethoxy compound was prepared in 96% yield in the same manner.

1-Alkoxy-3-carbomethoxy-4-piperidones (V). To a refluxing suspension of 54 g. (2.25 moles) of sodium hydride (as a 50% suspension in mineral oil) in 1200 ml. of benzene was added at once about one fifth of 208 g. (0.90 mole) of *N*-ethoxy-*N*-bis(β-carbomethoxyethyl)amine (III). The evolution of hydrogen started after 30 min. and the remaining ester was now added within 30 min. The gas evolution had subsided after another 30 min. of reflux. The mixture was cooled to room temperature and poured into 1500 ml. of ice water. The layers were separated and the benzene washed twice with 200 ml. of diluted potassium hydroxide solution. The combined aqueous layers were freed from benzene with 200 ml. of ether and were made neutral by careful addition of hydrochloric acid. An oil separated and was extracted with three 500-ml. portions of ether. The extract was dried over sodium sulfate and the ether evaporated. The colorless residue furnished upon distillation over a short Vigreux column 137 g. (71%) of 1-ethoxy-3-carbomethoxy-4-piperidone, b.p. 129°/14 mm. A sample of this compound gave a deep violet color with aqueous ferric chloride.

The corresponding 1-methoxy-3-carbomethoxy-4-piperidone was prepared in the same way in 75% yield.

1-Alkoxy-4-piperidones (VI). For the decarboxylation there is no need to isolate the pure β-keto ester. The alkaline solution of the crude compound, prepared as described above from 233 g. (1.0 mole) of the bisester III, was treated with an excess of hydrochloric acid and refluxed for 10 hr. Only a faint color with ferric chloride was left. The cooled solution was made alkaline with solid sodium carbonate and finally some sodium hydroxide and was extracted with seven 250-ml. portions of ether. The dried extract afforded upon distillation 106 g. (74%) of 1-ethoxy-4-piperidone, b.p. 86°/18 mm.

The corresponding 1-methoxy-4-piperidone can be prepared in the same manner in 60% yield. Physical properties and analytical data of these compounds are recorded in Table III.

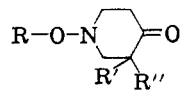
1-Alkoxy-3-methyl-4-piperidones (VII). (*A*) *From N-alkoxy-N-β-carbomethoxyethyl-N-β-carbomethoxypropylamines* (IV). The piperidones were prepared as described above by condensation of the corresponding bisesters (IV) with sodium hydride; the yield of 1-methoxy-3-methyl-4-piperidone was 92% and the yield of 1-ethoxy-3-methyl-4-piperidone was 74%.

(*B*) *By methylation of 1-alkoxy-3-carbomethoxy-4-piperidones* (V). *1-Alkoxy-3-methyl-3-carbomethoxy-4-piperidones* (VIII). A 100.5-g. sample (0.50 mole) of 1-ethoxy-3-carbomethoxy-4-piperidone was added within 15 min. with stirring to a warm solution of 0.50 mole of potassium ethylate, prepared by dissolving 19.5 g. of potassium metal in 250

(10)(a) A. H. Beckett, A. E. Cary, and G. Kirk, *J. Med. Pharm. Chem.*, 1, 17 (1959); (b) F. R. Ahmed, W. H. Barnes, and G. Kartha, *Chem. Ind.*, 485 (1959).

TABLE III

1-ALKOXY-4-PIPERIDONES



R	R′	R″	Formula	B.P./Mm.	Calcd.			Found		
					C	H	N	C	H	N
CH_3	H	H	$C_6H_{11}NO_2$	73°/12	55.79	8.58	10.85	55.42	8.55	10.92
C_2H_5	H	H	$C_7H_{13}NO_2$	86°/18	58.72	9.15	9.78	59.00	9.36	9.65
CH_3	CH_3	H	$C_7H_{13}NO_2$	76°/12	58.72	9.15	9.78	58.83	9.23	9.45
C_2H_5	CH_3	H	$C_8H_{15}NO_2$	82°/14	61.12	9.62	8.91	61.33	9.69	8.59
CH_3	H	$COOCH_3$	$C_8H_{13}NO_4$	118°/12	51.33	7.00	7.48	51.02	6.90	7.19
C_2H_5	H	$COOCH_3$	$C_9H_{15}NO_4$	129°/14	53.72	7.51	6.96	53.77	7.54	6.92
CH_3	CH_3	$COOCH_3$	$C_9H_{15}NO_4$	122°/14	53.72	7.51	6.96	54.12	7.73	6.73
C_2H_5	CH_3	$COOCH_3$	$C_{10}H_{17}NO_4$	124°/12	55.80	7.96	6.51	56.06	8.05	6.27

ml. of anhydrous ethanol. The yellow solution was cooled to room temperature without delay to avoid precipitation of the potassium salt of the β-keto ester and 71.0 g. (0.50 mole) of methyl iodide in 50 ml. of ethanol was added over a period of 1 hr. A slightly exothermic reaction took place and potassium iodide separated gradually. The mixture was refluxed for two additional hours, cooled to room temperature, filtered and evaporated in a rotating vacuum evaporator to a viscous oil. This was shaken with 200 ml. of saturated aqueous solution of sodium carbonate. The mixture was extracted with three 200-ml. portions of ether and the extract was washed with 100 ml. of 2*N* potassium hydroxide to remove starting material. The ethereal solution was dried over sodium sulfate and the ether distilled. The yellow residue furnished upon distillation 87.5 g. (81%) of 1-ethoxy-3-methyl-3-carbomethoxy-4-piperidone, b.p. 124°/12 mm.

The corresponding 1-methoxy compound was prepared in 75% yield in the same way. Both compounds gave no color with aqueous ferric chloride; physical and analytical data are recorded in Table III.

1-Alkoxy-3-methyl-4-piperidones (VII). For the decarboxylation 87.5 g. (0.41 mole) of 1-ethoxy-3-methyl-3-carbomethoxy-4-piperidone was dissolved in 300 ml. of 10% hydrochloric acid and kept at 85° for 12 hr. The solution was cooled to room temperature and made alkaline with solid sodium carbonate. Extraction with five 100-ml. portions of ether followed. The dried extract furnished upon distillation 56 g. (88%) of 1-ethoxy-3-methyl-4-piperidone, b.p. 82°/14 mm. The infrared spectra of this compound and the corresponding one prepared by method A were identical.

The decarboxylation of 1-methoxy-3-methyl-3-carbomethoxy-4-piperidone produced 1-methoxy-3-methyl-4-piperidone in 88% yield. The physical and analytical data are recorded in Table III.

1-Alkoxy-4-phenyl-4-hydroxypiperidines. (A) *Without substituent in the 3-position* (IX). *1-Methoxy-4-phenyl-4-hydroxypiperidine.* A solution of phenyllithium was prepared in the usual way from 5.6 g. (0.80 g.-atom) of lithium metal in 500 ml. of anhydrous ether and 63 g. (0.40 mole) of bromobenzene. To this was added a solution of 35 g. (0.27 mole) of 1-methoxy-4-piperidone in 100 ml. of ether as fast as the vigorously refluxing ether permitted. The mixture was refluxed for 30 additional min., cooled to room temperature and 100 ml. of water was added carefully. The ether layer was separated and extracted with five 50-ml. portions of 2*N* hydrochloric acid. This acidic solution was made alkaline with solid sodium carbonate and extracted with three 200-ml. portions of ether. The extract was dried overnight and evaporated to 200 ml. A crystalline hydrochloride separated upon addition of an excess of hydrochloric acid in anhydrous ethanol. Recrystallization from anhydrous ethanol furnished 55 g. (85%) of pure 1-methoxy-4-phenyl-4-hydroxypiperidine hydrochloride, m.p. 140°.

The free base was obtained in 97% yield by dissolving the hydrochloride in water and slow addition of excessive aqueous potassium hydroxide. The solid was filtered, washed with water, and dried over sulfuric acid. Recrystallization from petroleum ether (b.p. 60–90°) afforded the pure 1-methoxy-4-phenyl-4-hydroxypiperidine, m.p. 77°.

The analogous 1-ethoxy compound was prepared in the same way in a yield of 93%. The physical and analytical data are to be found in Table IV.

(B) *With substituent in the 3-position* (X). *α- and β-1-methoxy-3-methyl-4-phenyl-4-hydroxypiperidine.* The reaction of 1-methoxy-3-methyl-4-piperidone with phenyl-lithium in the way described above furnished a quantitative yield of an oily mixture of the isomeric 1-methoxy-3-methyl-4-phenyl-4-hydroxypiperidines. A 166-g. sample of this mixture was dissolved in 500 ml. of anhydrous ether and treated with an excess (80 ml.) of anhydrous alcoholic hydrochloric acid. The oily hydrochloride was allowed to settle overnight and the supernatant liquid was decanted. Crystallization occurred upon addition of 400 ml. of boiling acetone. The mixture was filtered while still hot and the crystals were washed with cold acetone. This hydrochloride was named the β-isomer; the yield was 48.3 g. (25%), m.p. 178°. Recrystallization from ethanol did not alter this melting point.

The mother liquor from the β-hydrochloride was evaporated to dryness *in vacuo*. The semisolid residue was dissolved in 300 ml. of water and made alkaline by adding diluted aqueous potassium hydroxide. The free bases were extracted with four 200-ml. portions of ether; the extract was dried and evaporated. The oily residue crystallized partially upon treatment with 100 ml. of petroleum ether (b.p. 60–90°). Filtration furnished 60 g. (36%) of the pure α-isomer, m.p. 61°, unchanged after recrystallization from petroleum ether. The mother liquor from the α-isomer was again converted to the hydrochlorides and the separation process was repeated. In this way the total yields were as follows: 63.5 g. (34.9%) of the β-1-methoxy-3-methyl-4-phenyl-4-hydroxypiperidine hydrochloride and 88.5 g. (53.3%) of the α-1-methoxy-3-methyl-4-phenyl-4-hydroxypiperidine; total yield 88.2%.

The free base of the β-isomer was prepared as follows: 25 g. of the β-hydrochloride was dissolved in 200 ml. of water and treated with an excess of aqueous potassium hydroxide. The separated oil was extracted with ether. Distillation furnished 21.0 g. (97%) of β-1-methoxy-3-methyl-4-phenyl-4-hydroxypiperidine as a colorless viscous oil, b.p. 135°/1 mm.

The free base of the α-isomer, m.p. 61°, proved to be the less stable one of two crystal modifications. During a recrystallization from ether the stable modification, m.p. 93°, was formed, which is much less soluble in petroleum ether. It was possible to precipitate the high melting form

TABLE IV

SUBSTITUTED 1-ALKOXY-4-HYDROXYPIPERIDINES

R	R′	R″	Formula	Isomer	M.P. B.P./Mm.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Hydrochlorides M.P.	Hydrochlorides Calcd. C	Hydrochlorides Calcd. H	Hydrochlorides Calcd. N	Hydrochlorides Found C	Hydrochlorides Found H	Hydrochlorides Found N
CH_3	H	C_6H_5	$C_{12}H_{17}NO_2$	—	77	69.54	8.27	6.76	69.41	8.11	7.05	140	59.11	7.44	5.75	58.88	7.29	5.63
CH_3	CH_3	C_6H_5	$C_{13}H_{19}NO_2$	α	61	70.55	8.65	6.33	70.61	8.80	6.27	135	60.57	7.82	5.43	60.59	7.84	4.96
CH_3	CH_3	C_6H_5	$C_{13}H_{19}NO_2$	α	93	70.55	8.65	6.33	70.27	8.35	6.18							
CH_3	CH_3	C_6H_5	$C_{13}H_{19}NO_2$	β	135/1	70.55	8.65	6.33	70.20	8.65	6.29	178	60.57	7.82	5.43	60.66	7.85	5.33
C_2H_5	H	C_6H_5	$C_{13}H_{19}NO_2$	—	65	70.55	8.65	6.33	70.21	8.31	6.54	164	60.57	7.82	5.43	60.47	7.85	5.09
C_2H_5	H	n-C_4H_9	$C_{11}H_{23}NO_2$	—	128/12	65.63	11.52	6.96	65.25	11.41	7.26	107	55.55	10.17	6.07	55.64	10.29	5.86
C_2H_5	CH_3	C_6H_5	$C_{14}H_{21}NO_2$	α	81	71.45	9.00	5.95	71.24	8.69	6.05	157	61.68	8.16	5.15	61.97	8.31	4.76
C_2H_5	CH_3	C_6H_5	$C_{14}H_{21}NO_2$	β	140/3	71.45	9.00	5.95	71.21	9.30	6.29	179	61.68	8.16	5.15	61.96	8.23	4.81

from a solution of the low melting one by seeding but the reverse was impossible. Both modifications furnished upon treatment with hydrochloric acid in ether the same hydrochloride, m.p. 135°.

α- and β-1-ethoxy-3-methyl-4-phenyl-4-hydroxypiperidine. A crude mixture of the isomeric 1-ethoxy-3-methyl-4-phenyl-4-hydroxypiperidines was produced in 96% yield by the reaction of 1-ethoxy-3-methyl-4-piperidone and phenyllithium in the described way. The separation of the isomers could be achieved by the same procedure as described above for the corresponding methoxy compounds. The yields were 28% of the β-1-ethoxy-3-methyl-4-phenyl-4-hydroxypiperidine hydrochloride and 50% of the α-1-ethoxy-3-methyl-4-phenyl-4-hydroxypiperidine; total yield 78%. The physical and analytical data of the bases and their hydrochlorides are compiled in Table IV.

1-Ethoxy-4-n-butyl-4-hydroxypiperidine. A 68.5-g. sample (0.5 mole) of freshly distilled *n*-butyl bromide was added dropwise to 7.0 g. (1.0 mole) of finely chopped lithium metal in 500 ml. of ether in such a rate as to keep the mixture gently refluxing. The air in the apparatus had been replaced by dry nitrogen. A solution of 48 g. (0.34 mole) of 1-ethoxy-4-piperidone in 50 ml. of ether was added after 30 additional min. of reflux. An excess of diluted hydrochloric acid was added carefully after another hour. The aqueous layer was separated and was made alkaline with diluted sodium hydroxide solution. The separated oil was extracted with three 250-ml. portions of ether; the extract was dried and the ether distilled. The main product distilled after a small forerun of starting material at 127–132°/12 mm.; redistillation furnished 42 g. (63%) of pure 1-ethoxy-4-*n*-butyl-4-hydroxypiperidine, b.p. 128°/12 mm. The *hydrochloride* was prepared with ethereal hydrochloric acid and was recrystallized from acetone/ether, m.p. 107°. The analytical data are recorded in Table IV.

Propionylation of the 1-alkoxy-4-phenyl-4-hydroxypiperidines. 1-Methoxy-4-phenyl-4-propionoxypiperidine and 1-propionyl-4-phenyl-4-hydroxypiperidine. A solution of 10.35 g. (0.05 mole) of 1-methoxy-4-phenyl-4-hydroxypiperidine in 39 g. (0.3 mole) of propionic anhydride was heated for 46 hr. to 95°. The excess of reagent was distilled *in vacuo* at the same temperature. The viscous brown residue was shaken with 150 ml. of a saturated sodium carbonate solution and the mixture was extracted with four 100-ml. portions of ether. A solid precipitated during this operation and was filtered and washed with ether. The combined ether layers were reextracted with four 50-ml. portions of 2*N* hydrochloric acid. The remaining ether was evaporated and the semisolid residue was combined with the filtered solid. Recrystallization from acetone furnished 2.2 g. (23%) of 1-propionyl-4-phenyl-4-hydroxypiperidine, m.p. 171°. This compound is insoluble in aqueous acids as well as in aqueous alkali.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.10; H, 8.15; N, 6.17.

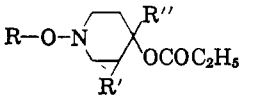
Infrared absorption was found at 3.0 (−OH), 3.45 (C—H), and 6.2 μ (C=O amide).

The aqueous acidic extract from above was made alkaline with solid sodium carbonate. An oil separated and was extracted with three 100-ml. portions of ether. This extract was dried with sodium sulfate and was evaporated to 100 ml. A crystalline hydrochloride precipitated upon addition of alcoholic hydrochloric acid; recrystallization from ethanol furnished 4.4 g. (30%) of 1-methoxy-4-phenyl-4-propionoxypiperidine hydrochloride, m.p. 139°. A small amount of starting material could be recovered from the mother liquors.

1-Ethoxy-4-phenyl-4-hydroxypiperidine was submitted to the same reaction and furnished 27% of the pure 1-ethoxy-4-phenyl-4-propionoxypiperidine hydrochloride, m.p. 132°, as well as 17% of 1-propionyl-4-phenyl-4-hydroxypiperidine, m.p. 171°. The analytical data of the hydrochlorides are recorded in Table V.

TABLE V

HYDROCHLORIDES OF VARIOUS 1-ALKOXY-4-PROPIONOXYPIPERIDINES



+ HCl

R	R'	R''	Formula	Isomer	M.P. B.P./Mm.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	H	C_6H_5	$C_{15}H_{22}ClNO_3$	—	139°	60.09	7.40	4.70	59.73	7.31	5.05
CH_3	CH_3	C_6H_5	$C_{16}H_{24}ClNO_3$	α	132°	61.22	7.71	4.46	61.24	8.12	4.37
CH_3	CH_3	C_6H_5	$C_{16}H_{24}ClNO_3$	β	112°	61.22	7.71	4.46	60.80	7.53	4.14
C_2H_5	H	n-C_4H_9	$C_{14}H_{27}NO_3$[a]	—	144°/12	65.33	10.57	5.44	65.48	10.66	5.80
C_2H_5	H	C_6H_5	$C_{16}H_{24}ClNO_3$	—	132°	61.22	7.71	4.46	61.33	7.70	4.75
C_2H_5	CH_3	C_6H_5	$C_{17}H_{26}ClNO_3$	α	155°	62.27	7.99	4.27	62.13	7.82	4.00
C_2H_5	CH_3	C_6H_5	$C_{17}H_{26}ClNO_3$	β	130°	62.27	7.99	4.27	62.42	8.23	4.05

[a] Free base, no crystallized hydrochloride obtained.

Propionylation of 1-ethoxy-4-n-butyl-4-hydroxypiperidine. A solution of 10.0 g. (0.05 mole) of 1-ethoxy-4-*n*-butyl-4-hydroxypiperidine in 30 g. (0.24 mole) of propionic anhydride was heated to 100° for 20 hr. The brown mixture was cooled to room temperature and poured into an excess of aqueous sodium carbonate solution. The separated oil was extracted with four 50-ml. portions of ether and the dried extract was evaporated. The residue furnished upon distillation over a short Vigreux column 8.7 g. (68%) of the desired ester, b.p. 144°/12 mm. No amide could be detected.

The *hydrochloride* was prepared in ether and did not crystallize. Analytical data in Table V.

Propionylation of the 1-alkoxy-3-methyl-4-phenyl-4-hydroxypiperidines (X). (A) *Reaction of the lithium salt with propionic anhydride. α-1-Ethoxy-3-methyl-4-phenyl-4-propionoxypiperidine.* A solution of 0.1 mole of methyl-lithium was prepared in the usual manner from 1.4 g. (0.2 mole) of lithium metal in 250 ml. of ether and 14.2 g. (0.2 mole) of methyl iodide. To this was added without delay a solution of 20.0 g. (0.085 mole) of α-1-ethoxy-3-methyl-4-phenyl-4-hydroxypiperidine in 250 ml. of ether. After the evolution of methane had subsided 22.1 g. (0.17 mole) of propionic anhydride was added within 20 min. A solid separated immediately. The turbid mixture was refluxed with stirring for 2 more hr. Diluted aqueous potassium hydroxide, 250 ml., was added carefully. The ether layer was separated and extracted with five 80-ml. portions of 2*N* hydrochloric acid. The acidic extract was made alkaline with solid sodium carbonate and extracted with four 100-ml. portions of ether. Evaporation of the dried extract furnished 20.6 g. of an orange oil which contained some unchanged starting material according to the infrared spectra.

The oil was dissolved in 200 ml. of anhydrous ether and treated with an excess of alcoholic hydrochloric acid. An oily salt precipitated which crystallized upon warming with a small amount of acetone. Repeated recrystallizations from acetone ether furnished 5.8 g. (21%) of the pure α-1-ethoxy-3-methyl-4-phenyl-4-propionoxypiperidine hydrochloride, m.p. 155°. The mother liquor contained an unseparable mixture of this compound and unchanged starting material. Analytical data in Table V.

(B) *Reaction of the magnesium salt with propionyl chloride. α-1-Methoxy-3-methyl-4-phenyl-4-propionoxypiperidine.* A Grignard solution was prepared from 3.7 g. (0.15 mole) of magnesium turnings in 250 ml. of ether and 21.5 g. (0.15 mole) of methyl iodide. To this was added within 20 min. a solution of 22.1 g. (0.10 mole) of α-1-methoxy-3-methyl-4-phenyl-4-hydroxypiperidine in 250 ml. of ether. Methane was evolved. The solution was refluxed for 10 min. and a solution of 13.9 g. (0.15 mole) of propionyl chloride was added within 15 min. The yellow mixture was refluxed for 10 additional min. Water, 250 ml., was added carefully and the ether was separated. The aqueous layer was washed with 100 ml. of ether; the combined ethereal solution was extracted with five 100-ml. portions of 2*N* hydrochloric acid. The extract was immediately treated with an excess of solid sodium carbonate and the separated oil was taken up in five 100-ml. portions of ether. This extract furnished upon evaporation 25.3 g. of a red oil which was free from starting material according to the infrared spectra. The *hydrochloride* was prepared in ether and was recrystallized from acetone-ether. The yield of the pure α-1-methoxy-3-methyl-4-phenyl-4-propionoxypiperidine hydrochloride, m.p. 132°, was 21.0 g. (67%). The analytical data are recorded in Table V.

Degradation of the α-1-alkoxy-3-methyl-4-phenyl-4-hydroxypiperidines (X). *α-1-Propionyl-3-methyl-4-phenyl-4-hydroxypiperidine* (XIV). A solution of 18.8 g. (0.08 mole) of α-1-ethoxy-3-methyl-4-phenyl-4-hydroxypiperidine in 62.5 g. (0.48 mole) of propionic anhydride was heated to 95° for 40 hr. A distinct aldehyde odor was noticeable during the reaction. The excess of anhydride was distilled at the same temperature under reduced pressure. The residue was poured into an excess of diluted aqueous potassium hydroxide. A solid separated and was filtered; the filtrate was extracted with ether. This extract furnished upon evaporation and conversion of the residue into the hydrochloride 9.7 g. (45%) of unchanged starting material hydrochloride, m.p. 157°. The filtered solid was recrystallized from 10 ml. of anhydrous ethanol. 5.3 g. (27%) of pure α-1-propionyl-3-methyl-4-phenyl-4-hydroxypiperidine, m.p. 161°, was obtained. This compound is insoluble in aqueous acids as well as in aqueous alkali.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.53; H, 8.28; N, 5.77.

The main infrared absorptions (potassium bromide-pellet) are at 2.95; 3.4; 6.2; 6.9; 8.3; 9.95; 13.1 and 14.2 μ.

A sample of α-1-methoxy-3-methyl-4-phenyl-4-hydroxypiperidine was submitted to the same reaction. α-1-Propionyl-3-methyl-4-phenyl-4-hydroxypiperidine, 34%, could be isolated from the reaction mixture; 39% of the starting material was recovered.

α-3-Methyl-4-phenyl-4-hydroxypiperidine (XV). A suspension of 2.47 g. (10 mmoles) of α-1-propionyl-3-methyl-4-phenyl-4-hydroxypiperidine in 50 ml. of 2*N* sodium hydroxide was refluxed for 20 hr. The solid liquefied gradually. The mixture was cooled to room temperature and was extracted with four 100-ml. portions of ether. The base was obtained by reextraction with four 50-ml. portions of 2*N* hydrochloric acid, alkalinization with sodium hydroxide and extraction with ether. Evaporation of the final extract furnished 1.5 g. (79%) of a colorless solid, m.p. 130–131°.

Recrystallization from petroleum ether (b.p. 60–90°) gave 1.1 g. pure α-3-methyl-4-phenyl-4-hydroxypiperidine, m.p. 132°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.12; H, 9.06; N, 7.64.

Main infrared absorptions (potassium bromide-pellet): 3.0; 3.4; 6.9; 9.9; 13.2 and 14.3 μ.

A sample of the compound was converted into the *hydrochloride*, m.p. 180° after recrystallization from ethanol-ether. This hydrochloride is only sparingly soluble in acetone.

Anal. Calcd. for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.27; H, 7.98; N, 5.85.

α-1,3-Dimethyl-4-phenyl-4-hydroxypiperidine (XVI). α-3-Methyl-4-phenyl-4-hydroxypiperidine, 570 mg., 3.0 mmoles, was dissolved in a mixture of 380 mg. (7.5 mmoles) of 90% formic acid, 330 mg. (3.3 mmoles) of 30% aqueous formaldehyde and 2.0 ml. of water. This solution was refluxed for 8 hr. An excess of hydrochloric acid was added and the mixture was evaporated at 35° under reduced pressure in a rotating evaporator. The residue was dissolved in 10 ml. of water and was made alkaline with potassium hydroxide. An oil precipitated and was extracted with three 15-ml. portions of ether. Evaporation of the dried extract furnished a crystalline residue, m.p. 98–100°, which gave upon recrystallization from 2 ml. of ligroin (b.p. 60–90°), 0.56 g. (91%) of pure α-1,3-dimethyl-4-phenyl-4-hydroxypiperidine, m.p. 100° (reported m.p. 100–101°) either alone or in mixture with an authentic sample.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.00; H, 9.28; N, 6.86.

The main absorptions in the infrared (potassium bromide-pellet) were at 3.2; 3.45; 3.6; 6.85; 6.95; 7.3; 7.8; 8.2; 8.7; 8.9; 9.1; 9.7; 10.0; 13.2 and 14.2 μ; this spectrum was superimposable with that of an authentic sample.

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CHARLOTTESVILLE, VA.

[CONTRIBUTION FROM PFISTER CHEMICAL WORKS, INC., AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Pyrimidines. I. Some Halogenated Monomethylpyrimidines

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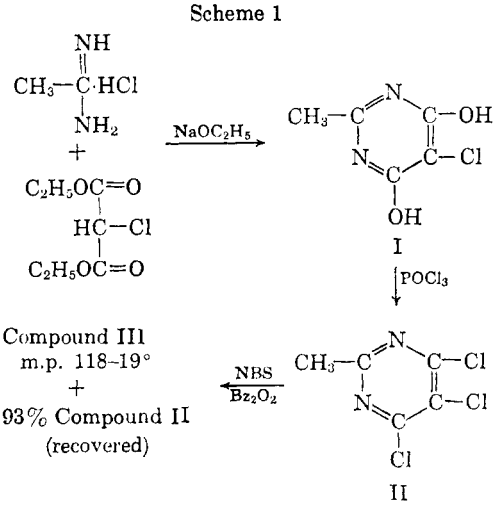
The three monomethyltrichloropyrimidines and intermediates were prepared. A study was made of the bromination of the methyl groups with *N*-bromosuccinimide.

In the course of preparing potential metabolite antagonists, the three monomethyltrichloropyrimidines and related compounds were produced. A further study was made of the bromination of the methyl groups with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide (Bz_2O_2).

The 2-methylpyrimidine analogs were prepared by condensing acetamidine with ethyl chloromalonate in the presence of sodium ethylate to yield 5-chloro-2-methylpyrimidine-4,6-diol. This on treatment with phosphorus oxychloride yielded 2-methyl-4,5,6-trichloropyrimidine, as indicated in Scheme 1. On treatment with *N*-bromosuccinimide the expected 2-bromomethyl-4,5,6-trichloropyrimidine was not obtained; however, a small yield of a compound was gotten which contained bromine, but has not, as yet, been completely characterized.

Scheme 1



To circumvent the problem of the bromination of 2-methyl-4,5,6-trichloropyrimidine with *N*-bromosuccinimide, an alternate approach to preparing the 2-halogenomethyl-4,5,6-trichloropyrimidine was devised. As is shown in Scheme 2, benzoyl glycolamidine was condensed with ethyl chloromalonate in the presence of sodium ethylate and 5-chloro-4,6-dihydroxy-2-pyrimidinemethanol was produced. Upon treatment with phosphorus oxychloride and phosphorus pentachloride, 2-chloromethyl-4,5,6-trichloropyrimidine was obtained.

5-Methyl-2,4,6-trichloropyrimidine was prepared by the method of Gerngross[3] and on bromination with *N*-bromosuccinimide a quantitative yield of 5-bromomethyl-2,4,6-trichloropyrimidine was obtained.

Since this work was completed, it was reported by Hasegawa[4] that 5-bromomethyl-2,4,6-trichloro-

(1) Part of this work was taken from the Ph.D. thesis of of H. Gershon, University of Colorado, 1950.

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(3) O. Gerngross, *Ber.*, **38**, 3394 (1905).

(4) M. Hasegawa, *Pharm. Bull. (Japan)*, **1**, 387 (1953) [*Chem. Abstr.*, **49**, 10970 (1955)].