

one crystallization from a minimum amount of methyl alcohol. The ethyl ester was prepared in a similar manner, and similar yields (Table I) were obtained when larger quantities were prepared.

1-Benzenesulfonylisonipecotylhydrazine.—To a refluxing mixture of 8 g. (0.24 mole) of hydrazine (95%) and 10 cc. of methyl alcohol was added rapidly dropwise a solution of 15.18 g. (0.054 mole) of methyl 1-benzenesulfonylisonipecotate in 125 cc. of methyl alcohol. The solution was refluxed for two hours and then distilled to one-half its volume. The crystalline product which separated on standing was filtered with suction and washed sparingly three times with methyl alcohol, yield 14.0 g. (Table I). It was purified for analysis by crystallization from 100 cc. of alcohol. The

yield obtained from the ethyl ester was only 50% of the theoretical.

1-Benzenesulfonylisonipecotylurea from the Acid Chloride.—A mechanically stirred mixture of 8.5 g. (0.14 mole) of powdered urea and the acid chloride from 3 g. (0.011 mole) of 1-benzenesulfonylisonipecotic acid was heated gradually to 130° where it was maintained for one hour. After cooling the cake was disintegrated by 50 cc. of hot alcohol and the solid was filtered from the cold mixture; yield 3.0 g., m.p. 204–205°. It was purified by dissolution in a hot mixture of 65 cc. of alcohol and 17 cc. of water. The hot filtrate was cooled finally in a salt-ice-bath whereupon it crystallized in the form of colorless fine needles.

NEWARK, DELAWARE

CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF LAKESIDE LABORATORIES, INC.]

Antispasmodics. II. Derivatives of N-Substituted-3-piperidols

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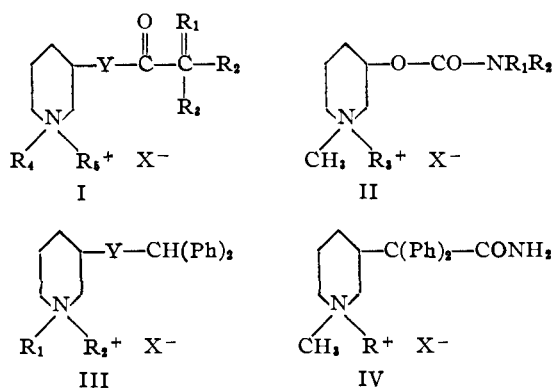
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The initial finding that the replacement of diethylaminoethyl by N-ethyl-3-piperidyl in some standard antispasmodic agents yielded compounds of superior spasmolytic activity prompted a more general investigation of the therapeutic usefulness of a variety of 3-piperidyl derivatives. Five classes of compounds were synthesized: (1) substituted acetic acid esters of 3-hydroxypiperidine and 3-mercaptopyperidine derivatives; (2) substituted carbamates of N-methyl-3-hydroxypiperidine; (3) N-substituted-3-piperidyl benzhydryl ethers, as well as their thioisosteres; (4) *p*-aminobenzoates of N-alkyl-3-piperidol; (5) N-methyl-3-piperidyl diphenylmethyl derivatives $R-C(Ph)_2Y$; $Y = CONH_2, CN$. The first series of compounds yielded a number of potent antispasmodic agents, of which the disubstituted hydroxyacetates appeared to be the most promising ones. The carbamates in series (2) either inhibited or potentiated acetylcholine spasms in the guinea pig ileum depending on the type of substituent. The benzhydryl ethers (series 3) were active spasmolytic agents. Quaternization of the nitrogen produced a tenfold increase in spasmolytic activity. The compounds in series (4) were local anesthetics comparable to procaine in potency. The diphenylacetamide derivatives (5) were moderate antispasmodics. Phenyl-2-thienylglycolic acid was obtained *via* a mixed benzoin condensation followed by a benzylic acid type rearrangement. The preparation of 3-mercaptopyperidines is described. A general method for obtaining N-aryl-substituted carbamates was developed.

A new amino alcohol has always been a challenge to the medicinal organic chemist for the synthesis of therapeutically useful derivatives. The ready availability of N-alkyl-3-hydroxypiperidines by the method of Paul and Tchelitcheff¹ prompted a long-range investigation in these laboratories of N-substituted-3-piperidyl derivatives as substitutes for the aminoalkyl portion in a large variety of physiologically active compounds.

The first paper in this series² dealt exclusively with substituted acetic acid esters of N-alkyl-3-hydroxypiperidines. Several of these derivatives have since been shown to be pharmacologically potent antispasmodic agents^{3–6} and clinically efficacious drugs in the treatment of gastrointestinal spasms.^{7–10} The present paper is a report on the chemistry and preliminary pharmacology on five

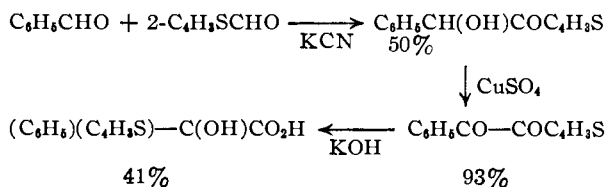
types of 3-piperidyl derivatives: (1) substituted acetic acid esters (I, $R_1 = H, OH, CH_2OH$; $R_2 = H, phenyl, 2-thienyl, cyclohexyl, cyclopentyl$; $R_3 = H, phenyl, n-propyl$; $R_4 = methyl, ethyl, isopropyl, n-butyl, 2-phenylisopropyl$; $R_5 = H, methyl, n-butyl$; $X = Cl, Br, I, citrate$; $Y = O, S$);



- (1) R. Paul and S. Tchelitcheff, *Compt. rend.*, **221**, 560 (1945).
- (2) J. H. Biel, H. L. Friedman, H. A. Leiser and E. P. Sprengeler, *This Journal*, **74**, 1485 (1952).
- (3) J. Y. P. Chen and H. Beckman, *J. Pharmacol. Exptl. Therap.*, **104**, 269 (1952).
- (4) J. Y. P. Chen, *Federation Proc.*, **13**, 343 (1954).
- (5) P. L. Ewing and L. D. Seager, *J. Pharmacol. Exptl. Therap.*, **106**, 385 (1952).
- (6) J. P. Long and H. H. Keasling, *Federation Proc.*, **13**, 380 (1954).
- (7) H. Necheles, H. Laski, L. D. Elegant and R. Baum, *Am. J. Digestive Diseases*, **21**, 121 (1954).
- (8) B. Weinberg, R. Ginsberg and H. Sorter, *ibid.*, **20**, 230 (1953).
- (9) F. Steigmann and R. A. Dolehide, *Federation Proc.*, **13**, 408 (1954).
- (10) N-Ethyl-3-piperidyl diphenylacetate hydrochloride (JB305), Dactil Lakeside Laboratories, is marketed as a general antispasmodic.

(2) disubstituted carbamates (II, $R_1 = methyl, n-butyl, phenyl$; $R_2 = methyl, n-butyl, phenyl, benzyl$; $R_3 = H, CH_3$; $X = Cl, Br, I$); (3) benzhydryl ethers (III, $R_1 = methyl, ethyl$; $R_2 = H$ or methyl; $X = Cl, Br$; $Y = O, S$); (4) *p*-aminobenzoates of N-alkyl-3-hydroxypiperidine; (5) N-alkyl-3-piperidyl diphenylmethyl derivatives (IV, $R = H, CH_3$; $X = Br, mono- or dihydrogen citrate$). The substituted acetic acid esters were prepared by

methods reported in the literature.¹¹⁻¹³ Phenyl-2-thienylglycolic acid, however, was synthesized by a more practicable method which involved a mixed benzoin condensation of benzaldehyde with 2-thiophenylaldehyde followed by a benzoic acid type rearrangement



A similar method has recently been described for the preparation of phenyl-3-thienylglycolic acid.¹⁴ The 3-mercaptopiperidines were obtained by the condensation of the 3-chloro derivatives with thioacetic acid in refluxing isopropyl alcohol followed by a mild alkaline hydrolysis of the thioacetates and a continuous ether extraction of the neutral solution.

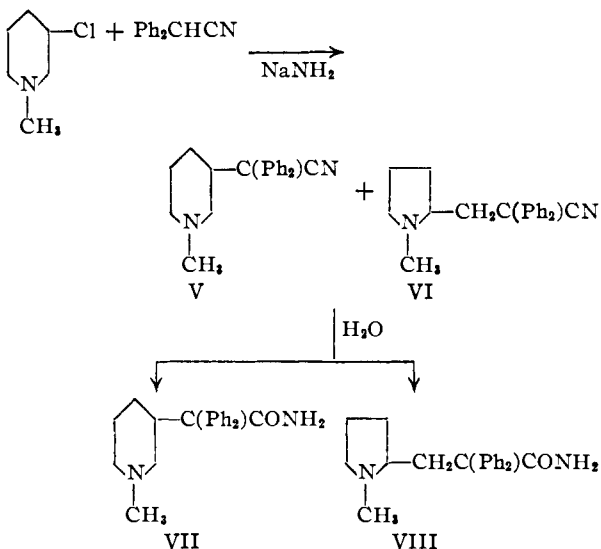
The synthesis of the esters was accomplished by treating (1) the acid chloride with the appropriate 3-hydroxypiperidine or 3-mercaptopiperidine in the presence of triethylamine in benzene, (2) the free acid with N-substituted-3-chloropiperidines in isopropyl alcohol or (3) the methyl ester of the acids with the amino alcohol in the presence of sodium methoxide and *n*-heptane by an ester interchange.¹⁵

A practical method for the synthesis of 3-piperidyl derivatives of N-aryl-substituted carbamates was developed which by-passed the use of phosgene as a starting material. The arylamine was allowed to react with sodium amide in toluene and the sodium salt condensed with methyl chlorocarbonate. The methyl carbamate was then subjected to an ester exchange reaction with N-methyl-3-hydroxypiperidine similar to method (3) described under the synthesis of the esters. The commercially available disubstituted carbamyl chlorides were treated with N-methyl-3-hydroxypiperidine in boiling pyridine to give a high yield of the desired 3-piperidyl carbamates.

The benzhydryl ether of N-methyl-3-hydroxypiperidine could be prepared either by treating the sodium salt of the amino alcohol with benzhydryl bromide or simply by the addition of benzhydryl chloride to a refluxing toluene solution of the amino alcohol. The latter method was preferred, as the yields were considerably higher. The preparation of the thiobenzhydryl ethers was accomplished by allowing benzhydrylthiouronium chloride to react with the N-alkyl-3-chloropiperidines in absolute ethanol.¹⁶ The *p*-aminobenzoate esters of the 3-piperidols were synthesized *via* the *p*-nitrobenzoate esters and subsequent catalytic reduction to the *p*-aminobenzoates.

For the preparation of α -(N-methyl-3-piperidyl)- α , α -diphenylacetamide the synthesis of the corre-

sponding piperidyl nitrile was undertaken. Diphenylacetone nitrile was allowed to react with N-methyl-3-chloropiperidine in the presence of sodium amide and toluene. The product was a semi-solid which defied crystallization. Conversion of the basic nitrile to its methobromide salt in ethyl alcohol yielded two isomeric fractions having melting points of 263–265° and 278–281°, respectively, and a mixed melting point of 238–242°. The bromide and nitrogen assays were identical for both compounds within the experimental limits. The mixed nitriles were subjected to hydrolysis with 90% sulfuric acid¹⁷ to the corresponding diphenylacetamides and two isomeric products isolated melting at 150–153° and 228–230° (VII, VIII). The methobromides of the two basic amides melted at 259–260° and 315–316°, respectively. The ring contraction of N-alkyl-3-chloropiperidine to N-alkyl-2-chloromethylpyrrolidine in basic medium has been described by Reitsema¹⁸ and it would be reasonable to assume that the condensation of diphenylacetone nitrile with N-methyl-3-chloropiperidine results in the formation of a 3-piperidyl diphenylacetone nitrile (V) and a 2-pyrrolidylmethyl diphenylacetone nitrile (VI).



the identity of the two isomers (V and VI) are now in progress.

All compounds were screened primarily for their spasmolytic activity against acetylcholine-induced spasms in the excised guinea pig ileum under the supervision of Mr. P. A. Nuhfer of our Pharmacology Division.

In the ester series the substituted hydroxyacetates afforded the most potent acetylcholine antagonists. The phenylpropylhydroxyacetate (no. 19) had one-tenth the activity of atropine. Replacing propyl by cyclohexyl (no. 17) doubled the activity, while replacement by a cyclopentyl radical (no. 18) increased potency sevenfold. The benzilate ester of N-methyl-3-hydroxypiperidine (no. 13) had about two-thirds the potency of atropine. Quaternization to the methobromide (no. 15) did not result in the usual increase in spasmolytic activity. The

(11) F. F. Blicke and M. U. Tsao, *THIS JOURNAL*, **66**, 1646 (1944).

(12) R. B. Moffett, C. A. Hart and W. H. Hoehn, *ibid.*, **69**, 1849 (1947).

(13) M. Rubin and H. Wishinsky, *ibid.*, **68**, 828 (1946).

(14) E. Campaigne and R. C. Bourgeois, *ibid.*, **75**, 2702 (1953).

(15) R. F. Feldkamp, *ibid.*, **74**, 3834 (1952).

(16) G. Rieveschl, U. S. Patent 2,483,436 (1949).

(17) M. E. Speeter, U. S. Patent 2,647,926 (1953).

(18) R. R. Reitsema, *THIS JOURNAL*, **71**, 2041 (1949).

phenyl-2-thienylhydroxyacetate of N-ethyl-3-piperidinol (no. 20) had 30% the activity of atropine. Two diastereoisomers were isolated from the synthesis of the corresponding N-methyl compound. While the higher melting isomer (no. 21) had twice the potency of atropine, the lower melting form had the same activity as the N-ethyl homolog (no. 20). The phenyl-2-thienylhydroxyacetate of diethylaminoethanol was reported as being equal to atropine in activity and three times as potent as the corresponding benzilate ester.¹⁹ This same relationship seems to hold true in the case of the N-methyl-3-piperidyl esters (no. 13 and 21). Lengthening the N-alkyl chain beyond two carbon atoms resulted in a sharp decrease of the antispasmodic effect. The *n*-butyl derivatives (no. 14 and 16) only had one-tenth to one-third the activity of the corresponding N-methyl compounds (no. 13 and 15).

Halpern²⁰ described the tropate ester of diethylaminoethanol to be one-seventh as potent as atropine. We found N-methyl-3-piperidyl tropate (no. 22) to have one-tenth the potency of atropine. Surprisingly low activity was also exhibited by the 1-cyclohexylcyclohexane carboxylate of N-ethyl-3-piperidinol (no. 23) which had one-hundredth the anticholinergic activity of atropine. The diethylaminoethyl ester of the above acid was reported²¹ as having one-eighth the activity of atropine. The cyclopentyl-*n*-propylacetate of N-ethyl-3-piperidinol (no. 24) was an effective acetylcholine antagonist at a dilution of 1:5,000,000. The diethylaminoethyl analog was found to be active at a dilution of 1:8,000,000 in inhibiting acetylcholine-induced spasms.²² The diphenylacetate esters were generally much less potent than the corresponding diphenylhydroxyacetates. The isosteric replacement of an "ester" oxygen by sulfur (no. 2) resulted in a twenty-fold activity increase over the parent compound (no. 1). Similarly, Dupré, *et al.*,²³ reported a twofold increase in spasmolytic activity of diethylaminoethyl diphenylthioacetate over the corresponding diphenylacetate ester. Replacement of N-methyl or N-ethyl by N-isopropyl (no. 5), 2-phenylisopropyl (no. 6) or *n*-butyl (no. 10) resulted in a sharp drop of the antiacetylcholine activity. These three derivatives had only one-fifth to one-tenth the potency of the parent compounds (no. 1, 3 and 7). The substitution of a phenyl by a cyclopentyl group in the acid moiety of compound no. 1 afforded a derivative (no. 12) having five times the spasmolytic potency of the parent compound.

The isosteric replacement of "CH" by "N" in compounds 3 and 7 yielded carbamate derivatives (no. 4 and 8) with sharply reduced activities; the benzyl phenyl carbamate (no. 9) appeared to be somewhat more potent.

The favorable antispasmodic properties of dimethylaminoethyl di-*n*-butylcarbamate ethyl sul-

fate²⁴ (Dibutoline) prompted the synthesis of a 3-piperidyl analog (no. 29). The latter proved to be a weak antispasmodic having only one-two hundredth the potency of atropine. The dimethylcarbamates of N-methyl-3-hydroxypiperidine hydrochloride and methobromide (no. 27 and 28) were inactive both as antispasmodics as well as spasmogens. However, the spasmogenic effect of acetylcholine was more than doubled when given in combination with compound 28. Hence, the latter resembles eserine in its mode of action.²⁵

The replacement of the diphenylacetoxo group in compounds 1, 3 and 7 by a thiobenzhydryl or benzhydryloxy radical produced ether derivatives (nos. 31-34) with equal or superior antispasmodic properties. Such structures might conceivably afford a longer duration of action being less subject to enzymatic hydrolysis. As antihistaminics the benzhydryl ethers were quite inactive in spite of their structural resemblance to diphenhydramine, the benzhydryl ether of dimethylaminoethanol.

N-Methyl-3-piperidyl acetate methiodide (no. 30) exhibited definite cholinergic properties.²⁶ Its spasmogenic effect on the guinea pig ileum was about one-hundredth that of acetylcholine and could be blocked completely by atropine.

The *p*-aminobenzoates of N-methyl- and N-ethyl-3-hydroxypiperidine (no. 25 and 26) were local anesthetic agents quite comparable to procaine in the initial screening tests.²⁵

The methobromides of the two isomeric diphenylacetamide derivatives were equally effective in antagonizing acetylcholine-induced spasms at ten times the dose of atropine. The citrate salt prepared from the lower melting isomer had the same activity as the methobromide. Hence, quaternization did not result in the usual increase in potency.

Acknowledgment.—We wish to thank Dr. H. L. Daiell for his continued interest and encouragement throughout the course of this project and Mr. E. F. Kluchesky for supplying the analytical data.

Experimental

2-Thienyl α -Phenyl- α -hydroxymethyl Ketone.²⁷—To a mixture of 21.2 g. (0.20 mole) of redistilled benzaldehyde and 22.4 g. (0.20 mole) of 2-thiophenecarboxaldehyde contained in 100 cc. of absolute ethanol was added 20 g. of potassium cyanide dissolved in 40 cc. of water. The mixture was stirred and refluxed for 1.5 hours. To the reaction mixture was then added 250 cc. of 50% aqueous ethanol and the solution refrigerated. The orange yellow precipitate was separated by filtration and washed repeatedly with water. The precipitate was then stirred in 10% sodium bicarbonate solution, again separated by filtration and washed by suspension in a dilute potassium carbonate solution. The solid was then washed thoroughly with water and recrystallized from aqueous ethyl alcohol; yield 21.5 g. (50%); m.p. 132-134°.

Anal. Calcd. for C₁₂H₁₀O₂S: S, 14.68. Found: S, 14.47.

Benz-2-thienyl.—A mixture containing 0.1 g. of cupric acetate, 5.0 g. (0.063 mole) of ammonium nitrate, 10.6 g. (0.05 mole) of 2-thienyl α -phenyl- α -hydroxymethyl ketone

(24) C. G. Peterson and D. R. Peterson, *Gastroenterology*, **5**, 169 (1945).

(25) We are indebted to Dr. F. W. Schueler, University of Iowa for the pharmacological evaluation of the carbamate derivatives and the *p*-aminobenzoic acid esters of the N-alkyl-3-hydroxy-piperidines.

(26) F. W. Schueler, *Arch. int. pharmacodynamie*, **93**, 417 (1953).

(27) The above structure is assigned to this compound on the basis of the subsequent reactions. No formal structure proof was carried out.

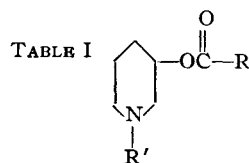
(19) F. F. Blicke and M. U. Tsao, *THIS JOURNAL*, **66**, 1645 (1945).

(20) B. N. Halpern, *Arch. intern. pharmacodynamie*, **59**, 149 (1938).

(21) C. H. Tilford, M. G. Van Campen and R. S. Shelton, *THIS JOURNAL*, **69**, 2902 (1947).

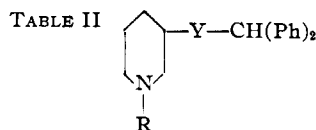
(22) R. B. Moffett, C. A. Hart and W. M. Hoehn, *ibid.*, **69**, 1849 (1947).

(23) S. Dupré, J. Levy and B. Tchoubar, *Compt. rend. soc. biol.*, **140**, 177 (1946).



No.	R	R'	°C.	Bases				Salts				M.p., °C.	Activity ^d atropine = 1.0	
				B.P. Mm.	Formula	Nitrogen, %		Salt	Nitrogen, %		Halogen, %			
						Calcd.	Found		Calcd.	Found	Calcd.	Found		
1	(C ₆ H ₅) ₂ CH ^a	C ₂ H ₅												0.01
2	(C ₆ H ₅) ₂ CH ^b	C ₂ H ₅			C ₂₁ H ₂₅ NOS	HCl	3.85	3.97	9.75	9.97	126-128	.20
3	(C ₆ H ₅) ₂ CH ^a	CH ₃						HCl						.01
4	(C ₆ H ₅) ₂ N	CH ₃	190-192	0.15	C ₁₉ H ₂₂ N ₂ O ₂	9.03	9.18	HCl	8.08	8.05	10.24	10.10	215-216	.001
5	(C ₆ H ₅) ₂ CH	CH(CH ₃) ₂	180-184	.55	C ₂₂ H ₂₇ NO ₂	4.15	4.16	HCl	3.75	3.80	9.50	9.37	134-136	.002
6	(C ₆ H ₅) ₂ CH Trasentine	CH(CH ₃)CH ₂ Ph			C ₂₃ H ₃₁ NO ₂			HCl	3.11	3.23	7.90	7.90	161-162	.0014 .01
7	(C ₆ H ₅) ₂ CH ^a	C ₂ H ₅						CH ₃ Br						.07
8	(C ₆ H ₅) ₂ N	CH ₃			C ₁₉ H ₂₂ N ₂ O ₂			CH ₃ Br	6.92	7.07	19.72	19.71	273-274	.001
9	C ₆ H ₅ C ₆ H ₅ CH ₂ } N	CH ₃	169-171	.025	C ₂₀ H ₂₄ N ₂ O ₂	8.64	8.73	CH ₃ Br	6.75	6.68	19.00	19.08	123-124	.006
10	(C ₆ H ₅) ₂ CH	<i>n</i> -C ₄ H ₉	188-191	.10	C ₂₃ H ₂₇ NO ₂	3.98	3.94	CH ₃ Br	3.14	3.32	17.93	17.88	143-145	.006
11	(C ₆ H ₅)(C ₆ H ₁₁)CH ^a	C ₂ H ₅						HCl						.06
12	(C ₆ H ₅)(C ₆ H ₉)CH	C ₂ H ₅	154-178	.04	C ₂₀ H ₂₉ NO ₂	HCl	3.98	4.15	10.10	10.13	181-183	.05
13	(C ₆ H ₅) ₂ COH	CH ₃	198-199	.20	C ₂₀ H ₂₃ NO ₃	4.31	4.25	HCl	3.88	3.76	9.81	9.78	221-223	.60
14	(C ₆ H ₅) ₂ COH	<i>n</i> -C ₄ H ₉	C ₂₃ H ₂₇ NO ₃	HCl	3.46	3.57	8.79	9.08		.06
15	(C ₆ H ₅) ₂ COH	CH ₃	C ₂₀ H ₂₃ NO ₃	CH ₃ Br	3.34	3.33	19.05	18.91	234-236	.50
16	(C ₆ H ₅) ₂ COH	<i>n</i> -C ₄ H ₉	C ₂₃ H ₂₈ NO ₃ ^a	CH ₃ Br	3.02	3.10	17.28	17.09	144-146	.20
17	(C ₆ H ₅)(C ₆ H ₁₁)COH	C ₂ H ₅	166-167	.05	C ₂₁ H ₃₁ NO ₃	4.06	4.02	HCl	3.67	3.66	9.30	9.11	215-217	.20
18	(C ₆ H ₅)(C ₆ H ₉)COH	C ₂ H ₅	201	.40	C ₂₀ H ₂₉ NO ₃	4.23	4.30	HCl	3.81	3.70	9.66	9.61	205-207	.75
19	(C ₆ H ₅)(<i>n</i> -C ₃ H ₇)COH	C ₂ H ₅	150	.10	C ₁₈ H ₂₇ NO ₃	4.59	4.50	HCl	4.10	3.88	10.40	10.30	166-167	.10
20	(C ₆ H ₅)(C ₄ H ₉ S)COH	C ₂ H ₅	C ₁₉ H ₂₃ NO ₃ S	HCl	3.67	3.67	9.30	9.19	181-182	.30
21	(C ₆ H ₅)(C ₄ H ₉ S)COH	CH ₃	C ₁₈ H ₂₁ NO ₃ S	HCl	3.81	3.74	9.67	9.57	227-228	2.0
22	C ₆ H ₅ CH(CH ₂ OH)	CH ₃	160-168	.10	C ₁₅ H ₂₁ NO ₃	5.32	5.18	H ₂ SO ₄	3.88	3.97	8.87 ^c	8.62 ^c	75 dec.	.10
23	(C ₆ H ₁₁)(C ₆ H ₁₀)-	C ₂ H ₅	151-161	.10	C ₂₀ H ₃₅ NO ₂	4.37	4.30	HCl	3.91	3.93	9.94	10.01	184-185	.01
24	(C ₅ H ₉)(<i>n</i> -C ₃ H ₇)CH	C ₂ H ₅	118-120	.03	C ₁₇ H ₃₁ NO ₂	4.99	5.13	HCl	4.41	4.44	11.19	11.05	116-118	.01
25	<i>p</i> -H ₂ NC ₆ H ₄	C ₂ H ₅	C ₁₄ H ₂₂ Cl ₂ N ₂ O ₂	HCl	9.86	9.57	12.50	12.52	120 dec.	
26	<i>p</i> -H ₂ NC ₆ H ₄	CH ₃	C ₁₃ H ₁₈ N ₂ O ₂	HCl	10.32	10.31	13.12	12.95	126 dec.	
27	(CH ₃) ₂ N	CH ₃	101-103	3.0	C ₉ H ₁₆ N ₂ O ₂	15.20	14.89	HCl	12.69	12.50	16.05	16.02	198-199	
28	(CH ₃) ₂ N	CH ₃	C ₉ H ₁₆ N ₂ O ₂	CH ₃ Br	10.01	9.95	28.65	28.44	205-206	.00005
29	(<i>n</i> -C ₄ H ₉) ₂ N	CH ₃	111-112	1.0	C ₁₅ H ₃₀ N ₂ O ₂	10.36	10.26	CH ₃ I	6.80	6.43	30.81	30.82	103-104	.005
30	CH ₃	CH ₃			C ₈ H ₁₆ NO ₂	8.92	8.62	CH ₃ I	4.68	4.41	42.49	42.87	171-172	

^a J. H. Biel, H. L. Friedman, H. A. Leiser and E. P. Sprengeler, THIS JOURNAL, 74, 1485 (1952). ^b Diphenylthioacetate. ^c Sulfur assay. ^d The compounds were screened for their spasmolytic activity against acetylcholine-induced spasms in the guinea pig ileum. * The melting points are all corrected.



No.	R	Y	Bases				Salts				M.p., °C.	Activity ^b atropine 1.0		
			B.P. °C.	Mm.	Formula	Nitrogen, % Calcd. Found	Salt	Nitrogen, % Calcd. Found	Halogen, % Calcd. Found					
31	CH ₃	O	160-161	0.11	C ₁₉ H ₂₃ NO	4.98	4.99	HCl	4.41	4.29	11.19	11.95	70 dec.	0.01
32	C ₂ H ₅	S	C ₂₀ H ₂₅ NS	HCl	4.03	4.27	10.19	10.43	145-146	.01
33	CH ₃	O	C ₁₉ H ₂₃ NO	CH ₃ Br	3.72	3.89	21.27	21.37	186-187	.10
34	C ₂ H ₅	S	C ₂₀ H ₂₅ NS	CH ₃ Br	3.45	3.41	19.66	19.68	153-161	.075

^a See footnote *c* in Table I. ^b See footnote *d* in Table I.

and 35 cc. of 80% aqueous acetic acid was refluxed with stirring for 1.5 hours, cooled in an ice-acetone bath and seeded with a crystal of the diketone. After crystallization appeared complete water was added to the mixture to precipitate any of the remaining diketone. The product was isolated by filtration and washed thoroughly with water; yield 10.1 g. (93%); m.p. 59-60°.

Anal. Calcd. for C₁₉H₂₃O₂S: S, 14.81. Found: S, 14.44.

Phenyl-2-thienylglycolic Acid.—To 15 g. of potassium hydroxide contained in 30 cc. of water was added 15.0 g. (0.069 mole) of phenyl 2-thienyl ketone dissolved in 30 cc. of 95% ethyl alcohol. The mixture was then refluxed for 10 minutes. The alcohol was distilled and the residual aqueous alkaline solution acidified with dilute hydrochloric acid. The precipitate was separated by filtration and washed with water. It was recrystallized from 100 cc. of benzene and decolorized with 5 g. of Darco. A white crystalline precipitate was obtained; yield 7.3 g. (41%), m.p. 127-129°. A mixed melting point with an authentic sample of the acid¹¹ showed no depression.

Anal. Calcd. for C₁₂H₁₀O₃S: S, 13.68. Found: S, 13.90.

The Synthesis of N-Alkyl-3-piperidyl Esters.—Three general procedures for the preparation of the piperidyl esters are described below.

Procedure A. N-Methyl-3-piperidyl Benzilate Hydrochloride (No. 13).—In a five-liter 3-necked flask equipped with an efficient stirrer, reflux condenser, Dean-Stark water-separator and a soda-lime tube were placed 3.0 liters of *n*-heptane, 230 g. (2.0 moles) of N-methyl-3-hydroxypiperidine and 484 g. (2.0 moles) of methyl benzilate. The mixture was stirred and heated to reflux. When all the methyl benzilate had dissolved, 10.0 g. of sodium methoxide was added to the refluxing solution in 2.0-g. portions during a period of 8-9 hours. At this time 75 cc. of methanol had separated and the transesterification was considered complete. The reaction mixture was concentrated to one-half its original volume and two liters of ether added to dissolve the ester. The ether-heptane solution was washed with six 500-cc. portions of water, dried with anhydrous potassium carbonate, filtered, and the solvent removed by distillation *in vacuo*. The oily residue was dissolved in 1,300 cc. of isopropyl alcohol and the solution acidified with ethereal hydrochloric acid. The crystalline solid was separated by filtration and 555 g. (74%) of the desired ester hydrochloride obtained; m.p. 221-223°.

Procedure B. *n*-Butyl-3-piperidyl Diphenylacetate Methobromide (No. 10).—To 8.0 g. (0.050 mole) of *n*-butyl-3-hydroxypiperidine and 6.0 g. (0.060 mole) of triethylamine in 50 cc. of benzene was added with stirring 11.5 g. (0.050 mole) of diphenylacetyl chloride dissolved in 50 cc. of benzene. The temperature of the reaction was not allowed to rise above 70° during the addition and was held there for an additional two hours. The triethylamine hydrochloride was separated by filtration and the filtrate fractionated *in vacuo*. The product was collected at 188-191° (0.10 mm.), yield 15.5 g. (88%). The methobromide was obtained in 75% yield by the addition of methyl bromide to an isopropyl alcohol solution of the basic ester, m.p. 143-145°.

Procedure C. N-Ethyl-3-piperidyl Phenylcyclohexylglycolate Hydrochloride (No. 17).—A mixture of 31.0 g. (0.13 mole) of phenylcyclohexylglycolic acid, 25.0 g. (0.17 mole) of N-ethyl-3-chloropiperidine and 70 cc. of anhydrous isopropyl alcohol was refluxed for 20 hours, the solvent removed by distillation and the residual oil neutralized with dilute aqueous hydrochloric acid. The acid solution was

extracted with ether to remove any unreacted acid and the aqueous phase made alkaline with sodium hydroxide solution. The alkaline mixture was extracted with ether and the ether extracts dried with potassium carbonate. The basic ester distilled at 166-167° (0.05 mm.); yield 24.0 g. (53%). The hydrochloride was prepared in 94% yield by the addition of ethereal hydrochloric acid to an acetone solution of the basic ester, m.p. 215-217°.

N-Methyl-3-piperidyl *p*-Nitrobenzoate Hydrochloride.—To 23.0 g. (0.20 mole) of N-methyl-3-hydroxypiperidine in 150 cc. of isopropyl alcohol was added slowly with stirring 37.0 g. (0.20 mole) of *p*-nitrobenzoyl chloride. After completion of the addition the mixture was stirred and refluxed for three hours. The reaction mixture was allowed to cool and the solid separated by filtration yielding 51 g. (85%) of crude ester hydrochloride, m.p. 170-180°. After recrystallization from ethyl alcohol, 32 g. (53%) of product was obtained, m.p. 218-219°.

Anal. Calcd. for C₁₈H₁₇ClN₂O₄: Cl, 11.82. Found: Cl, 11.73.

N-Methyl-3-piperidyl *p*-Aminobenzoate Hydrochloride (No. 26).—An alcoholic solution containing 15.0 g. (0.050 mole) of *p*-nitrobenzoate ester hydrochloride was reduced in the presence of 3.0 g. of 10% palladium-on-charcoal catalyst at a pressure of 60 lb. of hydrogen. The hydrogenation mixture was clarified by filtration and concentrated *in vacuo*. The oily *p*-aminobenzoate hydrochloride was crystallized from anhydrous ether, but defied recrystallization from any available solvent; yield 13.0 g. (96%), m.p. 126° (slow decomposition).

The Synthesis of N-Alkyl-3-piperidyl Carbamates.

Method A. N-Methyl-3-piperidyl N',N'-dimethylcarbamate Methobromide (No. 28).—A mixture containing 32.3 g. (0.30 mole) of dimethylcarbonyl chloride, 34.5 g. (0.30 mole) of N-methyl-3-hydroxypiperidine and 100 cc. of dry pyridine was refluxed for three hours, cooled and poured into 700 cc. of ice-water. The carbamate precipitated as a water-insoluble oil after the addition of solid sodium hydroxide and was extracted with ether from the alkaline mixture. The ether extracts were dried with potassium carbonate, the ether removed by distillation and the product collected at 101-103° (3.0 mm.); yield 44 g. (80%). The methobromide salt was prepared in 97% yield in acetone, m.p. 205-206°. The benzyl chloride salt was synthesized by adding 0.050 mole of benzyl chloride to an acetone solution containing 0.050 mole of the basic carbamate. The solution was allowed to stand for three weeks at room temperature and the precipitate collected by filtration; yield 7.0 g. (42%); m.p. 199-201°.

Anal. Calcd. for C₁₆H₂₅ClN₂O₂: Cl, 11.35; N, 8.96. Found: Cl, 11.41; N, 8.78.

Method B. (1) Methyl N-Phenyl-N-benzylcarbamate.—To 10.8 g. (0.28 mole) of sodium amide in 75 cc. of anhydrous toluene was added 36.6 g. (0.20 mole) of benzylaniline dissolved in 40 cc. anhydrous toluene. The mixture was stirred and refluxed for three hours and 19.1 g. (0.20 mole) of methyl chlorocarbonate in 40 cc. of toluene added. The mixture was stirred and refluxed for four hours, clarified by filtration and the filtrate fractionated *in vacuo*; b.p. 132-133° (0.035 mm.); yield 36.5 g. (76%).

Anal. Calcd. for C₁₅H₁₈NO₂: N, 5.81. Found: N, 6.04.

(2) N-Methyl-3-piperidyl N'-Phenyl-N'-benzylcarbamate (No. 9).—To 19.2 g. (0.167 mole) of N-methyl-3-hydroxypiperidine in 600 cc. of *n*-heptane was added 40.2 g.

(0.167 mole) of methyl phenylbenzylcarbamate. The reaction mixture was heated to reflux and 1.3 g. of sodium methoxide added. The methanol which distilled was separated in a Dean-Stark water separator. When no more methanol distilled over, the reaction mixture was concentrated to one-half its original volume and 300 cc. of ether added. A small amount of precipitate was removed by filtration, the filtrate washed with water and dried with potassium carbonate. The solvents were removed by distillation and the residual oil was fractionated *in vacuo*; b.p. 169–171° (0.025 mm.); yield 19.3 g. (36%).

N-Methyl-3-piperidyl Benzhydryl Ether (No. 31, 32). Method A.—To 2.3 g. (0.10 mole) of molten sodium in 150 cc. of hot toluene was added 11.5 g. (0.10 mole) of N-methyl-3-hydroxypiperidine. The solution was stirred and refluxed until all the sodium had dissolved. To this solution were then added 24.7 g. (0.10 mole) of benzhydryl bromide. Stirring and refluxing were continued for five hours and the reaction mixture clarified by filtration. The filtrate was extracted several times with 10% aqueous hydrochloric acid solution, the aqueous acid extract washed with ether and then made strongly alkaline with solid potassium hydroxide. The alkaline mixture was extracted with ether and the ether extracts dried with potassium carbonate. The product was collected at 160–161° (0.11 mm.); yield 4.5 g. (18%). The methobromide salt was prepared in isopropyl alcohol in 87% yield, m.p. 186–187°.

Method B.—A mixture of 40.4 g. (0.20 mole) of benzhydryl chloride and 46.0 g. (0.40 mole) of N-methyl-3-hydroxypiperidine in 100 cc. of toluene was stirred and refluxed for 24 hours. The reaction mixture was clarified by filtration and fractionated. The product was collected at 140–147° (0.08 mm.); yield 37.0 g. (66%). The methobromide salt was prepared in 87% yield and melted at 186–187°; a mixed melting point with the product obtained from Method A showed no depression.

N-Ethyl-3-piperidyl Thiobenzhydryl Ether Hydrochloride (No. 32).—To a well-stirred mixture of 25.1 g. (0.090 mole) of benzhydryl isothiuronium hydrochloride (0.090 mole) and 90 cc. of ethanol was added a solution of 13.5 g. (0.34 mole) of sodium hydroxide in 27 cc. of water. After stirring at approximately 40° for 0.5 hour a solution of 15.4 g. (0.084 mole) of N-ethyl-3-chloropiperidine hydrochloride in 75 cc. of ethanol was added and the mixture refluxed with stirring for two hours. The reaction mixture was cooled, poured into 500 cc. of water, the alkaline mixture extracted repeatedly with ether and the combined ether extracts dried with potassium carbonate. The solvent was removed by distillation and 23.1 g. (89%) of an oily residue remained which was too heat-labile to be distilled.

Anal. Calcd. for $C_{20}H_{25}NS$: N, 4.50; S, 10.29. Found: N, 4.53; S, 9.48.

The basic ether was converted to its hydrochloride salt in ether-isopropyl alcohol solution by the addition of ethereal hydrochloric acid, m.p. 145–146°.

N-Ethyl-3-piperidyl Thioacetate.—A mixture of 133 g. (0.90 mole) of N-ethyl-3-chloropiperidine and 69 g. (0.90 mole) of thioacetic acid in 500 cc. of anhydrous isopropyl alcohol was refluxed for 15 hours. After distillation of the isopropyl alcohol a mixture of 250 cc. of water and 400 cc. of ether was added to the oily residue. A solution of 134 g. of potassium carbonate in 200 cc. of water was added, the ether layer separated and the aqueous phase extracted repeatedly with ether. The combined ethereal extracts were dried with potassium carbonate, the ether removed by distillation and the residue distilled through a ten-inch Vigreux column; b.p. 66° (0.35 mm.), yield 87.4 g. (52%), n_{20}^D 1.4963.

Anal. Calcd. for $C_9H_{17}NOS$: S, 18.08; N, 7.90. Found: S, 17.33; N, 7.56.

N-Ethyl-3-mercaptopyperidine.—To 1200 cc. of a 6% aqueous sodium hydroxide solution was added with stirring at room temperature 88.3 g. (0.47 mole) of N-ethyl-3-piperidyl thioacetate and the mixture stirred at 20° for two hours. The solution was then neutralized with 94 cc. of glacial acetic acid saturated with 800 g. of ammonium sulfate and continuously extracted with ether. The ether extracts were distilled and the product collected at 57.5° (1.7 mm.), yield 39 g. (57%), n_{20}^D 1.4956.

Anal. Calcd. for $C_7H_{15}NS$: N, 9.64; SH, 22.82. Found: N, 9.89; SH, 23.56.

N-Ethyl-3-piperidyl *p*-Nitrothiobenzoate Hydrochloride.—To a solution of 11.7 g. (0.080 mole) of N-ethyl-3-mercapto-

piperidine in 25 cc. of toluene was added with stirring and cooling 14.8 g. (0.080 mole) of *p*-nitrobenzoyl chloride in 50 cc. of toluene. The solution was allowed to reflux for one-half hour, cooled and the crystalline hydrochloride separated by filtration. After two recrystallizations from isopropyl alcohol 19.3 g. (73%) of a white product was obtained, m.p. 149–151°.

Anal. Calcd. for $C_{14}H_{19}ClNO_3S$: Cl, 10.72; N, 8.47; S, 9.69. Found: Cl, 10.76; N, 8.61; S, 9.62.

The Reaction of N-Methyl-3-chloropiperidine with Diphenylacetoneitrile. (a).—A mixture containing 116 g. (0.60 mole) of diphenylacetoneitrile and 23.4 g. (0.60 mole) of sodium amide in 500 cc. of dry toluene was stirred with a Hershberg stirrer and allowed to reflux for six hours. To the hot mixture was then added 160 g. (1.20 moles) of N-methyl-3-chloropiperidine in 200 cc. of dry toluene. Stirring and refluxing were continued for 20 hours. The reaction mixture was cooled and extracted repeatedly with a 10% aqueous hydrochloric acid solution. The acid extracts were washed repeatedly with ether and the ether washings discarded. The aqueous acid phase was made alkaline by the addition of 200 g. of potassium hydroxide dissolved in 200 cc. of water. The alkaline mixture was extracted with ether, the ether extracts dried with anhydrous potassium carbonate and the ether removed by distillation. The residual oil was fractionated *in vacuo* and the product collected at 182–186° (0.05 mm.); yield 140 g. (80%).

Anal. Calcd. for $C_{20}H_{22}N_2$: N, 9.66. Found: N, 9.84.

(b) **Methobromides of Two Basic Diphenylacetoneitriles (A;B).**—To a solution of 58.0 g. (0.20 mole) of the basic nitrile (a) dissolved in 250 cc. of ethanol was added 19.0 g. (0.20 mole) of methyl bromide and the mixture allowed to stand at room temperature for three days. A white crystalline precipitate (fraction "A") was separated by filtration; yield 40.0 g., m.p. 259–261° dec. The filtrate was concentrated to dryness and the residue suspended in 200 cc. of isopropyl alcohol. The solid product (fraction "B") was separated by filtration yielding 33.0 g. of product, m.p. 255–263° dec. The isopropyl alcohol filtrate was evaporated to dryness and 4.5 g. of additional precipitate collected, m.p. 253–263°; total yield of solid, 76.5 g. (99.5%).

Fraction "A" was recrystallized twice from ethanol; yield 30.0 g., m.p. 263–265° dec.

Anal. Calcd. for $C_{21}H_{25}BrN_2$: Br, 20.75; N, 7.27; C, 65.50; H, 6.49. Found: Br, 20.65; N, 7.21; C, 65.77; H, 6.39.

Fraction "B" was recrystallized three times from isopropyl alcohol; yield 17.0 g., m.p. 278–281° dec.

Anal. Calcd. for $C_{21}H_{25}BrN_2$: Br, 20.75; N, 7.27; C, 65.50; H, 6.49. Found: Br, 20.61; N, 7.04; C, 65.30; H, 6.78.

A mixture of fractions "A" and "B" melted at 238–242° dec.

(c) **Basic Diphenylacetamides and their Methobromide Salts.**—To 500 cc. of 90% sulfuric acid solution was added 50 g. (0.17 mole) of the basic nitrile (a) and the solution heated for three hours on the steam-bath. The reaction mixture was poured onto ice, neutralized with 700 cc. of concd. ammonium hydroxide solution and extracted repeatedly with ether. A white solid precipitated during the extraction both in the organic and aqueous phase. It was separated by filtration and 6.4 g. of material collected, m.p. 216–224° (fraction "C"). The ether was removed by distillation, the residue suspended twice in 100 cc. of boiling acetone and 10.3 g. of solid isolated by filtration, m.p. 227–228° (fraction "D"). The combined acetone filtrates were evaporated to dryness and the oily residue crystallized from ether. Upon filtration of the ether suspension 5.2 g. of crystalline material was isolated, m.p. 150–153° (fraction "E").

Anal. Calcd. for $C_{20}H_{24}N_2O$: N, 9.10. Found: N, 9.04.

Fractions "C" and "D" were combined and recrystallized from a 5:1 mixture of chloroform and *n*-heptane; yield 6.0 g., m.p. 228–230° (fraction "F").

Anal. Calcd. for $C_{20}H_{24}N_2O$: N, 9.10. Found: N, 8.79.

To 3.08 g. (0.010 mole) of fraction "E" dissolved in 25 cc. of acetone and 5 cc. of isopropyl alcohol was added 0.95 g. (0.010 mole) of methyl bromide. The solid was collected by filtration; yield 3.90 g. (97%), m.p. 259–260° dec.

Anal. Calcd. for $C_{21}H_{27}BrN_2O$: Br, 19.83; N, 6.94. Found: Br, 19.86; N, 7.00.

To 2.5 g. (0.0075 mole) of fraction "F" dissolved in 25 cc. of ethanol was added 0.70 g. (0.0075 mole) of methyl bromide. The precipitate was separated by filtration; yield 1.8 g. (56%), m.p. 315–316° dec.

Anal. Calcd. for $C_{21}H_{27}BrN_2O$: Br, 19.83; N, 6.94. Found: Br, 19.93; N, 7.07.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. XII. Synthesis of Some 4- and 2,4-Substituted Pyrido[2,3-d]pyrimidines

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2-Aminonicotinic acid reacts with formamide, urea and thiourea to yield 4-hydroxy-(I), 2,4-dihydroxy-(IX) and 2-mercapto-4-hydroxy-(VI) pyrido[2,3-d]pyrimidines, respectively. These substances serve as starting materials for transformation reactions leading to a variety of pyrido-[2,3-d]pyrimidines with one or two functional groups in the pyrimidine moiety. Some similarities and differences between the pyrido[2,3-d]-pyrimidines and related quinazolines, pteridines and purines are pointed out.

The present investigation of pyrido(2,3-d)-pyrimidines was undertaken in connection with studies in this Laboratory of various pyrimidines and condensed pyrimidine systems as antagonists of the heterocyclic constituents of the nucleic acids², and of the folic-folinic acid family of vitamins.³ Prior to this work a few derivatives of pyrido-(2,3-d)pyrimidine were known. Klisiecki and Sucharda⁴ claim to have prepared 4-hydroxypyrido-(2,3-d)pyrimidine (I) from 2-aminonicotinic acid and formamide. McLean and Spring⁵ prepared 2,4-dihydroxypyrido(2,3-d)pyrimidine (IX) from quinolinic acid amide and sodium hypobromite. The structure of this compound was established by degradation to 2-aminonicotinic acid. These workers also obtained 2,4-dichloropyrido(2,3-d)-pyrimidine (XIV) from IX by chlorination with phosphorus oxychloride.

Attempts to prepare 4-hydroxypyrido(2,3-d)-pyrimidine (I) from 2-aminonicotinic acid and formamide according to the directions of Klisiecki and Sucharda⁴ resulted only in the recovery of a small amount of 2-aminonicotinic acid; the product described as melting above 385° was not obtained in any experiment. By increasing the amount of formamide and altering the reaction time, temperature and isolation procedure, a yield of over 70% of a product, m.p. 258°, could be obtained. This product analyzed correctly for 4-hydroxypyrido(2,3-d)pyrimidine (I) and possessed all the expected properties of this compound.

The synthesis of 2,4-dihydroxypyrido(2,3-d)-pyrimidine (IX) from the diamide of quinolinic acid was repeated in this Laboratory following the directions of McLean and Spring.⁵ The utility of this was limited by the low yield of the inter-

mediate. A search for another route led to the finding that the fusion of urea with 2-aminonicotinic acid gave IX in yields greater than 60% of the theoretical.

The need for rather large amounts of 2-aminonicotinic acid to prepare both I and IX resulted in a new preparation of this acid from the commercially available 2-amino-3-methylpyridine through oxidation of the acetyl derivative with potassium permanganate.

The reactions of 4-hydroxy- (I) and 2,4-dihydroxypyrido(2,3-d)pyrimidine (IX) with phosphoryl chloride and phosphorus pentasulfide provided chloro and mercapto derivatives which served as intermediates for a variety of transformation reactions. Thus 4-chloropyrido(2,3-d)pyrimidine (II) reacted readily with ammonia, diethylamine, aniline and hydrazine to give the 4-amino-(III), diethylamino- (VIII), anilino and hydrazino (IV) derivatives, respectively. The 2,4-dichloro derivative (XIV) readily yields various diamino derivatives (XIII, XVII, XVIII). It resembles 2,4-dichloroquinazoline⁶ in the selective replacement of the 4-chloro group under mild conditions. This led to the preparation of the 2-chloro-4-hydroxy (XI), 2-chloro-4-amino (XV) and 2-chloro-4-mercapto (XIX) derivatives.

Many of the derivatives were interrelated by transformation reactions which served to establish the structures. The allocation of functional groups in 2-chloro-4-hydroxypyrido(2,3-d)pyrimidine was established by its conversion to the 2-mercapto-4-hydroxy (VI) derivative which was also prepared in a definitive manner from 2-aminonicotinic acid and thiourea. The isomeric 2-hydroxy-4-mercapto derivative was obtained by hydrolysis of the 2-chloro-4-mercapto compound, providing confirmation of the structure assigned to these two derivatives. Mono- and dimercapto derivatives also could be prepared by treatment of the hydroxy derivatives with phosphorus pentasulfide. The dimercapto derivative (X) yielded the 2-mercapto-4-amino derivative (VII) which was hydrolyzed to VI, and, by treatment with Raney nickel, con-

(1) New Mexico Highlands University, Las Vegas, N. M.
 (2) G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell and H. VanderWerff, *Ann. N. Y. Acad. Sci.*, **52**, 1318 (1950); G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, M. B. Sherwood and H. VanderWerff, *J. Biol. Chem.*, **183**, 1 (1950).
 (3) G. H. Hitchings, G. B. Elion, H. VanderWerff and E. A. Falco, *ibid.*, **174**, 765 (1948); G. H. Hitchings, E. A. Falco and M. B. Sherwood, *Science*, **102**, 251 (1945); G. H. Hitchings, E. A. Falco, H. VanderWerff, P. B. Russell and G. B. Elion, *J. Biol. Chem.*, **199**, 43 (1952).
 (4) L. Klisiecki and E. Sucharda, *Roczniki Chem.*, **3**, 251 (1923); (*C. A.*, **19**, 721 (1925)).
 (5) A. C. McLean and F. S. Spring, *J. Chem. Soc.*, 2583 (1949).

(6) (a) F. J. Wolf, R. H. Beutel and J. R. Stevens, *THIS JOURNAL*, **70**, 4264 (1948); (b) F. H. S. Curd, J. K. Landquist and F. L. Rose, *J. Chem. Soc.*, 778 (1947).