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# Preparation and Properties of Hydroxyphenylalkylaminopyrimidines[1]

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*Received April 18, 1961*

Aminolysis of 2-chloropyrimidines with phenylalkanolamines provided a convenient route to a series of 2-(hydroxyphenylalkylamino)pyrimidines. Interestingly, 2-(β-hydroxyphenethylamino)pyrimidine (I) was also obtained when 2-aminopyrimidine was reacted with styrene oxide in the absence of added basic reagent. The isomeric 4-(β-hydroxyphenethylamino)pyrimidine (XI) was synthesized by reaction of 2,4-pyrimidinedithiol with β-hydroxyphenethylamine followed by Raney nickel desulfurization. The compounds have pronounced sedative-hypnotic and muscle relaxant (interneuronal blocking) properties but generally weak analgesic activity.

Interest in the analgesic and interneuronal blocking properties of 2-(β-hydroxyphenethylamino)pyridine[2-4] and related derivatives has prompted efforts to learn more concerning the structural features necessary to these pharmacological activities. The present paper deals with analogs in which the pyridine nucleus is replaced by a pyrimidine ring. This structural modification has afforded compounds with relatively little analgesic activity. Certain of the aminopyrimidine derivatives have, however, been found to be more potent interneuronal blocking agents than any in our experience; a few of the compounds also effectively produce general anesthesia in animals.[5,6]

The most generally applicable route used for the preparation of the 2-aminopyrimidine derivatives listed in Tables I and II involved the reaction of a 2-chloropyrimidine with the appropriate phenylalkanolamine. As was to be anticipated,[7] these reactions proceeded more smoothly and under much milder conditions than the corresponding aminolyses of 2-chloropyridine.[2] Although 2-chloropyrimidine readily underwent aminolysis in boiling benzene to provide 50–60% yields of products, better yields (up to 80%) were realized when the reactions were effected in boiling toluene. An equivalent of triethylamine was most satisfactorily used to neutralize the acid generated.

The reported, extreme instability of 4-chloropyrimidine[8] relative to the 2-isomer, paralleling behavior in the pyridine series and explicable in terms of the greater basicity of the 4-chloro derivatives, made it appear to be an unattractive intermediate to 4-aminopyrimidine analogs. In this regard it is interesting to note that 2,4-dichloro-(and diethoxy-)pyrimidine undergoes solvolysis and aminolysis to give mixtures of 2- and 4-substituted products, whereas 2,4-pyrimidinedithiol has been found to be selectively aminolyzed at the 4-position.[9] Several explanations have been offered for this (see ref. 9b). However, a recent report[10] (indicating that although 2,4-dichloropyrimidine reacts with methanol in non-discriminatory fashion, it reacts selectively with one equivalent of sodium methoxide to give 2-chloro-4-methoxypyrimidine in good yield) suggests that the differences observed in relative rates of reaction at the 2- and 4-position must to an important extent derive from changes in the detailed reaction process rather than from inherent differences in relative lability of substituents.[11]

The reaction of β-hydroxyphenethylamine with 2,4-pyrimidinedithiol went smoothly to give 4-(β-hydroxyphenethylamino)-2-pyrimidinethiol (IX) in 86% yield. This was converted to the 2-methylthio derivative (X) which was reduced to 4-(β-hydroxyphenethylamino)pyrimidine (XI) with Ra-

(1) Presented in part before the Division of Medicinal Chemistry at the 139th Meeting of the American Chemical Society, St. Louis, Mo., March 1961.

(2) A. P. Gray and D. E. Heitmeier, *J. Am. Chem. Soc.*, **81**, 4347 (1959); A. P. Gray, D. E. Heitmeier, and E. E. Spinner, *J. Am. Chem. Soc.*, **81**, 4351.

(3) T. B. O'Dell, L. R. Wilson, M. D. Napoli, H. D. White, and J. H. Mirsky, *J. Pharmacol. Exptl. Therap.*, **128**, 65 (1960).

(4) The generic name for this compound is phenyramidol.

(5) T. B. O'Dell *et al.*, to be published.

(6) Two of these, 2-(β-hydroxyphenethylamino)pyrimidine (I) and 2-(β-hydroxy-β,β-diphenylethylamino)pyrimidine (IV), are currently undergoing further evaluation as sedative-hypnotic agents.

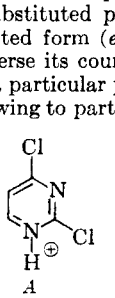
(7) See for example, N. B. Chapman and C. W. Rees, *J. Chem. Soc.*, 1190 (1954); R. R. Bishop, E. A. S. Cavell, and N. B. Chapman, *J. Chem. Soc.*, 437 (1952).

(8) M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1218 (1951).

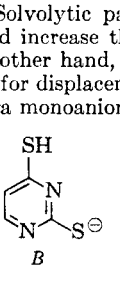
(9) (a) P. B. Russell, G. B. Elion, E. A. Falco, and G. H. Hitchings, *J. Am. Chem. Soc.*, **71**, 2279 (1949), and references cited therein; (b) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1004 (1951); (c) In our hands also, 2,4-dichloropyrimidine did not react with amines in a selective fashion.

(10) H. Yamanaka, *Chem. Pharm. Bull.* (*Tokyo*), **7**, 297 (1959) [*Chem. Abstr.*, **54**, 24782 (1960)].

(11) For example, a comparison of *p- vs. o*-quinonoid contributions to stabilization of a transition state would suggest that simple nucleophilic displacement would quite generally occur more rapidly at the 4- than at the 2- position of a 2,4-disubstituted pyrimidine. Solvolytic participation of a protonated form (*e.g. A*) would increase the reaction rate and reverse its course. On the other hand, the dithiol might have a particular predilection for displacement at the 4- position owing to participation of a monoanion (*B*).

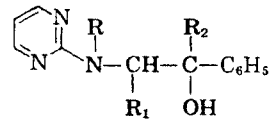


*A*



*B*

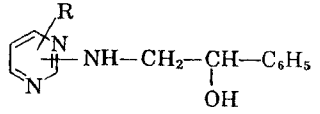
TABLE I. 2-AMINOPYRIMIDINES



| | R | $R_1$ | $R_2$ | Salt | M.P.[c] | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Chlorine, %[a] Calcd. | Chlorine, %[a] Found | Nitrogen, %[b] Calcd. | Nitrogen, %[b] Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | H | H | H | — | 92–93 | $C_{12}H_{13}N_3O$ | | | | | | | 6.51 | 6.46 |
| | | | | HCl | 167–168 | $C_{12}H_{14}ClN_3O$ | 57.25 | 57.45 | 5.60 | 5.47 | 14.09 | 14.06 | | |
| II | Methyl | Methyl | H | — | 97–99 | $C_{14}H_{17}N_3O$ | | | | | | | 5.76 | 5.80 |
| | | | | HCl[d] | 159–160 | $C_{14}H_{18}ClN_3O$ | 60.10 | 60.43 | 6.48 | 6.80 | 12.67 | 12.45 | | |
| III | H | Methyl | H | — | 123–124 | $C_{13}H_{15}N_3O$ | | | | | | | 6.11 | 6.09 |
| | | | | HCl | 165–166 | $C_{13}H_{16}ClN_3O$ | 58.78 | 58.66 | 6.07 | 5.98 | 13.35 | 13.15 | | |
| IV | H | H | Phenyl | — | 202–203 | $C_{18}H_{17}N_3O$ | | | | | | | 4.81 | 4.79 |
| | | | | HCl | 215 | $C_{18}H_{18}ClN_3O$ | 65.94 | 66.35 | 5.53 | 5.75 | 10.82 | 10.77 | | |
| V | H | Phenyl | H | — | 168–170 | $C_{18}H_{17}N_3O$ | | | | | | | 4.81 | 4.80 |
| | | | | HCl | 222–223 | $C_{18}H_{18}ClN_3O$ | 65.94 | 66.54 | 5.53 | 5.57 | 10.82 | 10.75 | | |
| VI | H | H | Ethyl | — | 141 | $C_{14}H_{17}N_3O$ | | | | | | | 5.76 | 5.79 |
| | | | | HCl | 155–156 | $C_{14}H_{18}ClN_3O$ | 60.08 | 60.73 | 6.48 | 6.37 | 12.67 | 12.65 | | |

[a] Potentiometric determination of ionic chlorine. [b] Basic nitrogen, by acetous-perchloric titration. [c] The salts melt with decomposition. [d] $[\alpha]_D^{25}$ +66.8 (*c*, 2.00 ethanol).

TABLE II. AMINOPYRIMIDINES

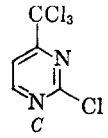


| | Isomer | R | Salt | M.P.[c] | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Chlorine, %[a] Calcd. | Chlorine, %[a] Found | Nitrogen, %[b] Calcd. | Nitrogen, %[b] Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IX | 4 | 2-SH | — | 191–193 | $C_{12}H_{13}N_3OS$ | | | | | | | 5.67 | 5.52 |
| | | | HCl | 207–209 | $C_{12}H_{14}ClN_3OS$ | 50.78 | 50.74 | 4.97 | 5.21 | 12.50 | 12.54 | | |
| X | 4 | 2-$SCH_3$ | — | 124–126 | $C_{13}H_{15}N_3OS$ | | | | | | | 5.36 | 5.33 |
| | | | HCl | 209 | $C_{13}H_{16}ClN_3OS$ | 52.43 | 52.72 | 5.41 | 5.38 | 11.90 | 11.93 | | |
| XI | 4 | H | HCl | 169–170 | $C_{12}H_{14}ClN_3O$ | 57.25 | 56.67 | 5.60 | 5.52 | 14.09 | 14.05 | | |
| XII | 4 | 2-OH | — | 218–219 | $C_{12}H_{13}N_3O_2$ | 62.33 | 61.89 | 5.66 | 5.78 | | | 6.04 | 6.01 |
| XIII | 4 | 2-$NH_2$ | — | 151–152 | $C_{12}H_{14}N_4O$ | | | | | | | 6.08 | 6.10 |
| | | | HCl | 179–180 | $C_{12}H_{15}ClN_4O$ | 54.04 | 54.31 | 5.67 | 5.25 | 13.30 | 13.26 | | |
| XIV | 2 | 4-$CCl_3$ | — | 110 | $C_{13}H_{12}Cl_3N_3O$ | | | | | | | 4.21 | 4.01 |
| | | | | | | | | | | | 9.05 | | |
| | | | HCl | 175–176 | $C_{13}H_{13}Cl_4N_3O$ | 42.31 | 42.19 | 3.55 | 3.52 | 9.60 | 9.69 | | |
| XV | 2 | 4-COOH | — | 203–205 | $C_{13}H_{13}N_3O_3$ | 60.22 | 60.28 | 5.05 | 5.03 | | | 5.40 | 5.31 |
| XVI | 2 | 4-$CH_3$ | — | 70–72 | $C_{13}H_{15}N_3O$ | | | | | | | 6.12 | 5.96 |
| | | | HCl | 139–140 | $C_{13}H_{16}ClN_3O$ | 58.78 | 58.96 | 6.07 | 6.01 | 13.35 | 13.24 | | |
| XVII | 2 | 4,6-di-$CH_3$ | — | 91–93 | $C_{14}H_{17}N_3O$ | | | | | | | 5.76 | 5.81 |
| | | | HCl | 108–110 | $C_{14}H_{18}ClN_3O$ | 60.10 | 59.94 | 6.48 | 6.36 | 12.67 | 12.71 | | |

[a] Potentiometric determination of ionic chlorine. [b] Basic nitrogen, by acetous-perchloric titration. [c] The salts melt with decomposition.

ney nickel. Attempts to prepare the 2-methylsulfonyl derivative by oxidation of X with hydrogen peroxide in glacial acetic acid afforded only starting material and (in poor yield) 4-(β-hydroxyphenethylamino)-2-pyrimidinol (XII), possibly arising from oxidative degradation of the initially formed sulfone. Treatment of IX with chloroacetic acid also gave XII.

Required 2-chloropyrimidines were obtained from the corresponding hydroxypyrimidines by standard procedures. Of particular interest was the report[9b] that 2-hydroxy-4-methylpyrimidine with phosphorus oxychloride alone afforded the expected 2-chloro derivative, but with a mixture of phosphorus oxychloride and pentachloride gave a tetrachloropyrimidine of unassigned structure. We have duplicated these results and have found the yield of tetrachloro derivative to depend strikingly on the amount of phosphorus pentachloride used. Use of two, three and four equivalents of pentachloride to one of the pyrimidine progressively increased the yield from *ca.* 10, to 40, to as high as 80%. The product is considered to be 2-chloro-4-trichloromethylpyrimidine (*C*) inasmuch as it reacted vigorously with β-hydroxyphenethylamine



*C*

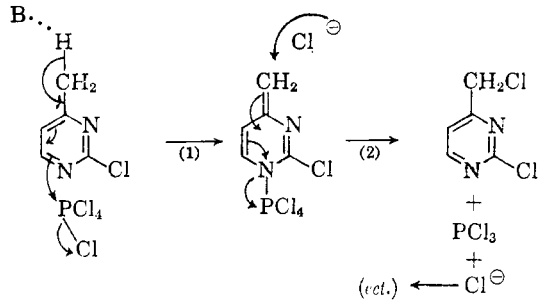
to give a trichloropyrimidine derivative (presumably (XIV) which underwent silver nitrate-promoted hydrolysis with loss of the three remaining chlorine atoms to yield a carboxylic acid (XV).[12]

In searching for an alternative approach to 2-(β-hydroxyphenethylamino)pyrimidine (I), the sodium salt of 2-aminopyrimidine was treated with styrene oxide under conditions similar to those proved satisfactory in the aminopyridine series.[2] Although alkylation of the sodium salt with alkyl halides has been of some applicability,[13] even prolonged boiling of the reactants in ethylene glycol dimethyl ether, in the present instance, provided only about 5% of I. This may be partly ascribed to the insolubility of the sodium salt and partly to the stability—and consequent lack of reactivity—of the aminopyrimidine anion. On the other hand, it has been shown that 2-methylaminopyrimidine may be obtained in excellent over-all yield by the simple reaction of 2-aminopyrimidine itself with methyl iodide in boiling ethanol[14] followed by treatment of the initially formed 1-methyl-2-pyrimidonimine with warm alkali which smoothly effects ring opening and recyclization on the exocyclic nitrogen.[15] Analogous behavior has been observed with other aminopyrimidine systems,[16] and Taylor and Loeffler[16] have suggested that the rearrangement involves initial nucleophilic attack of hydroxide ion on the pyrimidonimine.

The reaction of 2-aminopyrimidine with styrene oxide did yield 10–30% of I, presumably by rearrangement, but, in contrast to the methylation process, did not require the intervention of a strong hydroxylic base. Boiling of the reactants in ethanol[17] afforded 10–15% yields. Slightly better results were, in fact, realized when the reaction was carried out in a non-hydroxylic solvent, hot dimethylformamide, or in the absence of solvent at 120–130°. I could be isolated directly from these reactions and identified in the form of its hydrochloride salt, without being subjected to alkaline conditions. Treatment of the crude mixture of products obtained from any of these processes with hot alcoholic alkali[15] did not improve the yield. Indeed, the best yields of I (up to 32%) were obtained when 2-aminopyrimidine was treated with styrene oxide in boiling ethanol and this was followed by heating of the crude product mixture at 120–130°.

The present evidence shows that neither added alkali nor external hydroxylic solvent is required for this reaction. In attempting to elucidate the process, it is significant to note that although prolonged reaction times resulted in even lower yields, only small amounts of 2-aminopyrimidine could ever be recovered and a slow, steady evolution of ammonia was observed throughout the heating

(12) Mechanistic considerations would appear to be in accord with this formulation. Although a free radical process has not been unequivocally ruled out, the reaction proceeded equally well in the dark or under ultraviolet light. A plausible ionic course might involve:



This would account for the need for excess pentachloride and, if steps analogous to (1) were rate determining, for the fact that no products at an intermediate level of chlorination were encountered. (Step 1 should proceed more readily with the chloromethyl derivative, etc.). The reported conversion of 4-methylpyrimidine to its trichloromethyl derivative with molecular chlorine and sodium acetate in acetic acid [H. Bredereck, W. Jentzsch, and G. Morlock, *Chem. Ber.*, **93**, 2405 (1961)] could involve an analogous process in which chlorine becomes reduced to chloride.

(13) R. R. Adams and F. C. Whitmore, *J. Am. Chem. Soc.*, **67**, 735 (1945).

(14) C. G. Overberger and I. C. Kogon, *J. Am. Chem. Soc.*, **76**, 1065 (1954).

(15) D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 4035 (1955); D. J. Brown, *Nature*, **189**, 828 (1961).

(16) P. Brookes and P. D. Lawley, *J. Chem. Soc.* 539 (1960); E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960) and references cited therein.

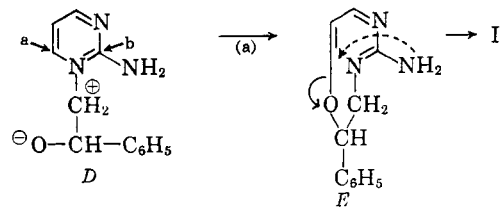
(17) Addition of a small amount of hydrochloric acid to the reaction medium had no deleterious effect.

TABLE III

| | Compound | $pK_a'$[a] | Relative Interneuronal Blocking Activity[b] | Relative Analgesic Activity[c] |
|---|---|---|---|---|
| I | 2-(β-Hydroxyphenethylamino)pyrimidine | 3.48 | 4+ | ± |
| IV | 2-(β-Hydroxy-β,β-diphenylethylamino)pyrimidine | 3.2 | 4+ | ± |
| XI | 4-(β-Hydroxyphenethylamino)pyrimidine | 5.41 | 1+ | 1+ |
| | 2-(β-Hydroxyphenethylamino)pyridine[d] | 5.85 | 3+ | 2+ |
| | 4-(β-Hydroxyphenethylamino)pyridine[e] | 8.49 | 0 | 1.5+ |

[a] Apparent dissociation constants were measured by titration of *ca.* 0.01*M* solutions of the hydrochloride salts in 60:40 dimethylformamide–carbon dioxide-free water with 0.1*N* sodium hydroxide at 25° using a Beckman Model G *p*H meter. [b] Relative activities are averages, based on the intravenous dose required to block polysynaptic (linguomandibular and flexor) reflexes in both anesthetized and decerebrate dogs. [c] Relative activities are based on the per cent increase in response time, to a radiant heat pain stimulus, of mice treated with 5 mg./kg. i.v. of drug (*cf.* ref. 3). [d] Phenyramidol.[2,3] [e] *Loc. cit.*[2,3]

period. Since 2-aminopyrimidine is perfectly stable under the conditions, it seems most reasonable to assume that relatively complete conversion to the pyrimidonimine is readily effected, and that this unisolated intermediate undergoes two competing reactions: (1) thermal rearrangement to I and (2) degradation with accompanying evolution of ammonia. The rearrangement must then involve intramolecular utilization of the hydroxyl group conveniently placed on the hypothesized pyrimidonimine intermediate. By analogy with the corresponding pyridonimine,[2] this intermediate can be considered to be at least in equilibrium with the zwitterion form (*D*) which could rearrange as indicated. Ammonia evolution could involve a corresponding reaction at (b). In this connection it might




be noted that ethylene and propylene oxides have been reported recently to react with 4-methyl-2-aminothiazole at 150° in the absence of solvent to give good yields of products substituted at the exocyclic nitrogen.[18]

*Biological properties.*[5,19] The series at hand invites a comparison of isosteric compounds. The most striking general pharmacological effect of the replacement of the pyridine nucleus by the pyrimidine in these compounds is the definite reduction in analgesic properties coupled with a marked increase in interneuronal blocking activities. This serves to reinforce the thesis that these activities are independent. As indicated in Table III, the principal physico-chemical effect of the introduction of a second nitrogen is a reduction in basicity. Although this is a severely restricted series, the biological activity profiles of the isosteres listed in Table III suggest a possible correlation with basic strength. As basicity is reduced, in proceeding from 4- to 2-aminopyridine and then from 4- to 2-aminopyrimidine, the ratio of interneuronal blocking to analgesic activity correspondingly increases. The guanidine derivative XVIII (a strong base), which might be considered as a ring-opened pyrimidine analog, was devoid of activity. It appears plausible that the effect of changes in basicity (and consequently in polarity and hydration) in this series of closely related compounds should be mainly on distribution of the agent in the animal organism. The weaker bases should be more capable of penetrating biological membranes. Further β-substitution on the phenethyl group did not, but α-substitution did reduce interneuronal blocking activity.

The most powerful interneuronal blocking agents in this series are I and the β,β-diphenyl analog IV, which at doses of 10 mg./kg., administered intravenously to an anesthetized dog, depress the polysynaptic linguomandibular and flexor reflexes by 80–100%. It is of particular interest that the same compounds are uniquely capable of inducing marked sedative-hypnotic effects. At intravenous doses of 30–40 mg./kg., I completely anesthetizes the dog for a period of about six minutes whereas IV puts the dog to sleep for fifty to seventy-five minutes.

## EXPERIMENTAL[20]

*Intermediates.* 2-Chloropyrimidine, m.p. 64–66°, was prepared by treatment of 2-hydroxypyrimidine hydrochlo-

(18) Yu. K. Yurév, K. Yu. Novitskiĭ, and M. N. Demina, *Zhur. Obshchcĭ Khim.*, **29**, 2299 (1959)[*Chem. Abstr.*, **54**, 9891 (1960)].

(19) We thank Dr. T. B. O'Dell and his associates for the data discussed here.

(20) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill., and by the Micro-Tech Laboratories, Skokie, Ill. Melting points are corrected for stem exposure.

ride,[21] m.p. 203–207°, with a mixture of phosphorus pentachloride and phosphorus oxychloride,[22] with phosphorus oxychloride alone[23] or with the addition of dimethylaniline. Yields averaged 40–45%. 2-Chloro-4-methylpyrimidine,[22] m.p. 46–48°, 2-chloro-4,6-dimethylpyrimidine,[22] m.p. 36–38°, and 2,4-dichloropyrimidine,[8] m.p. 61°, were prepared by reaction of the appropriate hydroxypyrimidine with phosphorus oxychloride in the absence of the pentachloride.

2,4-Pyrimidinedithiol,[9a,24] γ-hydroxy-γ-phenylpropylamine,[2] β-hydroxy-β,β-diphenylethylamine,[25] β-hydroxy-β,β-dibenzylethylamine,[25] β-hydroxy-α,β-diphenylethylamine,[26] m.p. 124–126°, β-hydroxy-β-ethyl-β-phenethylamine,[27] and 1-phenyl-2-ethylthiuronium bromide,[28] m.p. 108–109°; picrate, m.p. 196–198°, were prepared according to the literature. β-Hydroxyphenethylamine,[29] b.p. 118–120° (2 mm.), m.p. 53–55°; hydrochloride salt, m.p. 213–215°, was prepared by the hydrazinolysis of *N*-(β-hydroxyphenethyl)-phthalimide.[30]

2-Amino-4-chloropyrimidine was obtained from the American Cyanamid Co., New York 20, N.Y., *l*-ephedrine from J. H. DeLamar and Son, Inc., Chicago, Ill., and *dl*-norephedrine from the Gamma Chemical Corp., Great Meadows, N. J.

*2-Chloro-4-trichloromethylpyrimidine.* The published procedure[9b] was modified in that use of more phosphorus pentachloride was found to improve the yield markedly. A mixture of 51.0 g. (0.35 mole) of 2-hydroxy-4-methylpyrimidine hydrochloride (Aldrich Chemical Co.), 290 g. (1.4 moles) of phosphorus pentachloride and 92 ml. (1.0 mole) of phosphorus oxychloride was heated for 6 hr. at 130–135° (oil-bath temperature). The reaction mixture was concentrated under slightly reduced pressure to remove most of the excess phosphorus oxychloride, the residue was poured on cracked ice, and the resultant precipitate extracted with ether. Drying and removal of the ether left a dark oil which was distilled to yield 64.5 g. (80%) of product, b.p. 122–124° (10 mm.), solidified on standing, m.p. 43–46°; A sample, recrystallized from hexane, melted at 44–46° (lit.[9b] gives b.p. 132.5–134° (13 mm.), m.p. 43.5–45°, for "*2,x,x,x*-tetrachloro-4-methylpyrimidine").

*Reaction of 2-chloropyrimidines with phenylalkanolamines.* This method was most versatile and was used for preparing the 2-substituted compounds listed in the tables. A few examples will serve to illustrate the procedure.

A. *2-(β-Hydroxyphenethylamino)pyrimidine* (I). To a mixture of 62.1 g. (0.45 mole) of β-hydroxyphenethylamine, 55.6 g. (0.55 mole) of triethylamine and 200 ml. of toluene was added 54.5 g. (0.48 mole) of 2-chloropyrimidine. The mixture was heated, with stirring, in an oil bath at 130° for 6 hr. The warm mixture was filtered from 49.5 g. of triethylamine hydrochloride, m.p. 253–255°. Refrigeration of the toluene filtrate afforded a precipitate that was recrystallized from isopropyl alcohol to give a total of 78.1 g. (80% yield) of I, m.p. 92–93°.

The *hydrochloride salt* of I, recrystallized from ethyl alcohol, showed m.p. 167–168°.

B. *2-(γ-Hydroxy-γ-phenylpropylamino)pyrimidine* (VII). A stirred mixture of 7.4 g. (0.05 mole) of γ-hydroxy-γ-phenylpropylamine, 5.1 g. (0.05 mole) of triethylamine, 5.8 g. (0.05 mole) of 2-chloropyrimidine and 25 ml. of benzene was heated on the steam bath for 7 hr. and worked up as was I to yield, after crystallization from isopropyl alcohol, 6.6 g. (59%) of VII, m.p. 118–119°.

*Anal.* Calcd. for $C_{13}H_{15}N_3O$: N(basic), 6.11. Found: N(basic) 6.14.

The *hydrochloride salt of* VII, recrystallized from isopropyl alcohol-ether, showed m.p. 100–104°.

*Anal.* Calcd. for $C_{13}H_{16}ClN_3O$: C, 58.78; H, 6.07; Cl, 13.35. Found: C, 59.18; H, 6.08; Cl(ionic), 12.92.

C. *2-(β-Hydroxy-β,β-dibenzylethylamino)pyrimidine* (VIII). To a mixture of 20.5 g. (0.08 mole) of β-hydroxy-β,β-dibenzylethylamine, 10 g. (0.1 mole) of triethylamine and 75 ml. of dry toluene was added 10.3 g. (0.09 mole) of 2-chloropyrimidine. The mixture was heated and stirred in an oil bath at a temperature of 130° for 7 hr. The cooled reaction mixture was filtered, the collected precipitate was triturated with water and the residue dissolved in benzene. The benzene solution, combined with the toluene filtrate, was dried and evaporated *in vacuo* to leave a white solid which crystallized from isopropyl alcohol to give 14.1 g. (52%) of VIII, m.p. 128–129°.

*Anal.* Calcd. for $C_{20}H_{21}N_3O$: N(basic), 4.38. Found: N(basic) 4.37.

The *hydrochloride salt* of VIII recrystallized from isopropyl alcohol, showed m.p. 151–153°.

*Anal.* Calcd. for $C_{20}H_{22}ClN_3O$: C, 67.50; H, 6.23; Cl, 9.96. Found: C, 67.80; H, 6.02; Cl(ionic), 9.56.

D. *2-(β-Hydroxyphenethylamino-4-trichloromethylpyrimidine* (XIV). To a stirred mixture of 9.0 g. (0.06 mole) of β-hydroxyphenethylamine and 15 ml. (0.1 mole) of triethylamine was added 15.0 g. (0.06 mole) of 2-chloro-4-trichloromethylpyrimidine. The initial reaction was quite vigorous and cooling was necessary. The mixture was then warmed on the steam bath for 1 hr., taken up in chloroform and the resultant solution was washed with a 2% hydrochloric acid solution. The chloroform layer was dried and concentrated *in vacuo* and the residual solid was crystallized from isopropyl alcohol to give 15.2 g. (70%) of XIV, m.p. 109–110°.

*2-(β-Hydroxyphenethylamino)-4-carboxypyrimidine* (XV). To a solution of 6.6 g. (0.02 mole) of XIV in 75 ml. of acetic acid was added a solution of 17.0 g. (0.1 mole) of silver nitrate in 40 ml. of deionized water. The mixture was heated on the steam bath for 2 hr., filtered to remove silver chloride (7.4 g.) and the filtrate diluted with 600 ml. of deionized water to give 4.5 g. of a precipitate which was apparently the silver salt of XV. Hydrogen sulfide was bubbled into a suspension of the salt in 200 ml. of warm ethanol and the precipitated silver sulfide was removed. Refrigeration of the ethanol filtrate afforded 2.0 g. of light yellow powder which was recrystallized from ethanol to yield 1.5 g. (29%) of XV, m.p. 203–205° with evolution of carbon di-

(21) Obtained essentially as described by T. V. Protopopova and A. P. Skoldinov, *Zhur. Obshcheĭ Khim.*, **27**, 1276 (1957) [*Chem. Abstr.*, **52**, 3812 (1958)]. It should be noted that in order to obtain satisfactory material, it was necessary to boil the ethanol solution of urea and 1,1,3,3-tetramethoxy-(or ethoxy-)propane for 30 min. and then to recrystallize the product from boiling glacial acetic acid. At room temperature, as has also been reported by D. G. Crosby and R. V. Berthold, *J. Org. Chem.*, **25**, 1916 (1960), the product was found to contain high-melting impurities.

(22) T. Matsukawa and B. Ohta, *J. Pharm. Soc., Japan*, **69**, 489, 491 (1949) [*Chem. Abstr.*, **44**, 3455, 3456 (1950)].

(23) J. W. Copenhaver and R. F. Kleinschmidt, British Patent **663,302** (1951) [*Chem. Abstr.*, **46**, 10212 (1952)].

(24) H. L. Yale, *J. Am. Chem. Soc.*, **75**, 678 (1953).

(25) K. Thomas and F. Bettzieche, *Z. Physiol. Chem.*, **140**, 244 (1924) [*Chem. Abstr.*, **19**, 635(1925)].

(26) W. D. McPhee and E. S. Erickson, Jr., *J. Am. Chem. Soc.*, **68**, 626 (1946). This isomer has been assigned the *threo* configuration; see J. Weijlard, K. Pfister, III, E. F. Swanezy, C. A. Robinson, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 1216 (1951).

(27) M. Tiffeneau and H. Cahnmann, *Bull. soc. chim.* [5], **2**, 1876 (1935) [*Chem. Abstr.*, **30**, 1782 (1936)].

(28) A. Bertram, *Chem. Ber.*, **25**, 55 (1892), reports the picrate, m.p. 196°.

(29) A. Dornow and H. Theidel, *Chem. Ber.*, **88**, 1272 (1955), give m.p. 56–57°; hydrochloride salt, m.p. 212°.

(30) A. Terada, *Nippon Kagaku Zasshi*, **77**, 1265 (1956) [*Chem. Abstr.*, **53**, 5185 (1959)].

oxide,[31] soluble in dilute sodium bicarbonate with effervescence.

*Reaction of 2-aminopyrimidine with styrene oxide. 2-(β-Hydroxyphenethylamino)pyrimidine* (I). This reaction was extensively studied. In boiling ethanol (with or without the addition of a catalytic amount of hydrochloric acid, but without subsequent heating), yields averaged 10–15%. The following illustrates the most useful modification of this process.

To a boiling solution of 570 g. (6 moles) of 2-aminopyrimidine in 2 l. of ethanol was added 27 ml. of 37% hydrochloric acid (0.3 mole) and then, dropwise with stirring, 864 g. (7.2 moles) of styrene oxide. The solution was boiled under reflux for 30 hr., concentrated *in vacuo* and the residual oil was heated at 120–130° (pot temperature) for 3.5 hr. A slow evolution of ammonia was noted throughout the heating period. The reaction mixture was dissolved in methanol and the solution was acidified with ethereal hydrogen chloride and refrigerated. Recrystallization of the resultant precipitate from methanol afforded 488 g. (32%) of the *hydrochloride salt* of I, m.p. 167–169°. Admixture with authentic material prepared from 2-chloropyrimidine did not depress the melting point. The infrared spectra of the two samples were superimposable. From the methanol mother liquors, 76 g. (10%) of 2-aminopyrimidine was recovered in the form of its hydrochloride salt.

*Anal.* Calcd. for $C_{12}H_{14}ClN_3O$: Cl, 14.09. Found: Cl(ionic), 14.12.

Treatment of an aqueous solution of the I hydrochloride with aqueous ammonia in the cold gave I, m.p. 92–94° after recrystallization from isopropyl alcohol. A mixture melting point with authentic material was not depressed.

*4-(β-Hydroxyphenethylamino)-2-pyrimidinethiol* (IX). A mixture of 44.0 g. (0.32 mole) of β-hydroxyphenethylamine and 21.6 g. (0.15 mole) of 2,4-pyrimidinedithiol was heated in an oil bath at 120° for 2.5 hr. The semisolid residue was triturated with benzene and then with acetone to give 31.8 g. (86%) of IX, m.p. 191–193°.

*4-(β-Hydroxyphenethylamino)-2-methylthiopyrimidine* (X). To a solution of 31.0 g. (0.12 mole) of IX in 200 ml. of water containing 5.2 g. (0.13 mole) of sodium hydroxide was added, with stirring, 16.5 g. (0.13 mole) of dimethyl sulfate. The mixture was stirred for 1.5 hr. and the precipitated product was washed with water and crystallized from isopropyl alcohol to give 25.0 g. (88%) of X as white crystals, m.p. 124–126°.

*4-(β-Hydroxyphenethylamino)pyrimidine* (XI). A stirred mixture of 10.0 g. (0.04 mole) of X, 15 teaspoonfuls of Raney nickel catalyst (W-2) and 150 ml. of ethyl alcohol was heated on the steam bath for 4 hr. The filtered solution was concentrated *in vacuo* to a gum which was converted to the hydrochloride salt. Recrystallization from isopropyl alcohol gave 4.6 g. (56%) of the *hydrochloride salt* of XI, as colorless plates, m.p. 169–170°.

*4-(β-Hydroxyphenethylamino)-2-pyrimidinol* (XII). To a cooled solution of 9.3 g. (0.04 mole) of X in 100 ml. of glacial acetic acid was added, dropwise with stirring, 15 g. of 30% hydrogen peroxide (0.13 mole). After the solution had stood at room temperature for 5 days[32] it was diluted with ether and excess ethereal hydrogen chloride added to precipitate a yellow oil which could not be crystallized. An aqueous solution of the hydrochloride salt was treated with solid potassium carbonate and the resultant precipitate was recrystallized from a mixture of methyl and ethyl alcohol to give 1.2 g. of XII, m.p. 218–219°, soluble in dilute sodium hydroxide.

Reaction of IX with chloroacetic acid followed by treatment with concentrated hydrochloric acid also gave XII, m.p. and mixture m.p., 217–219°.

*2-Amino-4-(β-hydroxyphenethylamino)pyrimidine* (XIII). A mixture of 8.0 g. (0.06 mole) of 2-amino-4-chloropyrimidine, 9.0 g. (0.06 mole) of β-hydroxyphenethylamine, 7.0 g. (0.07 mole) of triethylamine in 50 ml. of ethanol was heated on the steam bath for 8 hr. The solution was concentrated *in vacuo* to a thick yellow oil which was triturated with water. The residual oil was dissolved in dilute hydrochloric acid, the acid solution was washed with ether, cooled and made basic with 20% sodium hydroxide to precipitate an oil which solidified. The white solid was crystallized from isopropyl alcohol to give 5.6 g. (40%) of XIII, m.p. 151–152°.

*β-Hydroxyphenethylguanidine hydrobromide* (XVIII). This compound was prepared according to the published procedure.[33] Recrystallization from isopropyl alcohol gave XVIII as a white crystalline powder, m.p. 140–142°.

*Anal.* Calcd. for $C_9H_{14}BrN_3O$: C, 41.56; H, 5.42; Br, 30.73. Found: C, 41.85; H, 5.47; Br(ionic), 30.55.

*Acknowledgment.* The authors are indebted to Mr. D. F. Cortright and to Miss M. Unroe for the basic nitrogen, ionic halogen and $pK_a$ determinations and to Mr. R. D. Garver and Mr. R. P. Ryan for technical assistance.

DECATUR, ILL.

(31) A drop of a saturated solution of calcium hydroxide, when held over the open end of the melting point capillary, gave a white precipitate.

(32) Shorter reaction times (5 to 24 hr.) gave only recovered X.

(33) H. C. Bhatnagar, N. N. Chopra, K. S. Narang, and J. N. Ray, *J. Indian Chem. Soc.*, **14**, 344 (1937) [*Chem. Abstr.*, **32**, 512 (1938)], prepared the hydriodide salt.