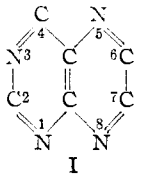
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

# Pyrimido[4,5-b]pyrazines. I. Synthesis of 6,7-Symmetrically Substituted Derivatives[1]

BY C. K. CAIN, M. F. MALLETTE AND E. C. TAYLOR, JR.

The pyrimido[4,5-b]pyrazine nucleus, I, is present in a number of naturally occurring substances.



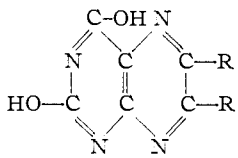
I

Among these may be mentioned xanthopterin, 2-amino - 4,6 - dihydroxypyrimido[4,5-b]pyrazine, and leucopterin, 2-amino-4,6,7-trihydroxypyrimido[4,5-b]pyrazine, which are pigments isolated from butterfly wings. The flavins, represented by riboflavin, are benzo derivatives of this same nucleus. It has been reported[2] that Vitamin $B_c$ or Folic Acid may contain this same nucleus. In addition to the biological significance of such compounds, Ellingson, *et al.*,[3] and Weijlard, *et al.*,[4] have shown that such compounds may serve as a convenient source of substituted pyrazines when the pyrimidine portion is cleaved by the action of acids or bases under strenuous conditions.

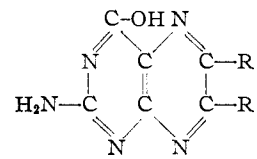
In view of the importance of such compounds, we have begun a study of the synthesis of a number of derivatives of the nucleus with a hope of improving the methods of synthesis of those compounds reported in the literature as well as the preparation of new compounds of possible biological or synthetic application. Since molecules of this type cannot in general be characterized satisfactorily by melting points, we have determined their ultraviolet absorption spectra.

The most general method of synthesis involves the use of a substituted pyrimidine as one of the reactants and formation of the pyrazine ring by reaction between 1,2-diamino groups and 1,2-dicarbonyl groups. Using this method, Kuhn and Cook[5] prepared 2,4-dihydroxypyrimido[4,5-b]pyrazine (for which they suggested the name lumazine) by interaction of 5,6-diamino-2,4-dihydroxypyrimidine and glyoxal. The same authors as well as Ganapti[6] varied the dicarbonyl compound to prepare several substituted lumazines. Recently Totter[7] has used a similar reaction to prepare leucopterin from 4-hydroxy-2,5,6-triaminopyrimidine salts and oxalic acid.

It will be noted that xanthopterin and leucopterin have an amino group in the 2-position while the lumazines have a hydroxyl group in that position. A search of the literature reveals few compounds having the 2-amino group present. In order to study the preparation of molecules of these types and the effect of various substituents on the ultraviolet absorption spectrum, we have prepared a series of compounds represented by formulas II and III where R = H, $CH_3$ or phenyl, as well as compounds having phenanthro and acenaphtho groups fused onto the pyrimidopyrazine nucleus.



II



III

A list of the compounds studied, together with the starting materials used in the preparation, solvent used for recrystallization and significant data from the ultraviolet absorption spectra of solutions in 0.1 *N* sodium hydroxide is included in Table I. Spectra of the diaminopyrimidines have been included for comparison.

Analytical samples of compounds 2–10 were used to prepare solutions for measurement of absorption spectra. Samples of compounds 1, 11 and 12 were purified by recrystallization from water and dried *in vacuo*.

The synthesis, properties and identification of isomers resulting from the reaction between diaminopyrimidines and unsymmetrical dicarbonyl compounds are to be subjects of forthcoming communications. Biological testing of the compounds described is in progress and will be reported elsewhere.

## Experimental

**5,6-Diamino-2,4-dihydroxypyrimidine Bisulfite.**—Our synthesis of this compound is essentially that of Bogert and Davidson.[8] Since the yield is appreciably better and the method involves fewer isolations of intermediates, the procedure is reported in detail.

To a solution of sodium ethoxide prepared by dissolving 92 g. (4 moles) of sodium in 2000 ml. of absolute ethanol, 120 g. (2 moles) of urea and 212 ml. (2 moles) of ethyl cyanoacetate were added. The mixture was refluxed for three hours on a hot water-bath. The solid which had precipitated was collected by filtration, washed thoroughly

(1) The work presented in this paper was supported in part by grants from the Nutrition Foundation, Inc., and from the Wyeth Institute of Applied Biochemistry. It represents a part of a collaborative project entitled "Newer Members of the B Group of Vitamins."

(2) Mitchell, THIS JOURNAL, **66**, 274 (1944); Bloom, Vandenbelt, Binkley, O'Dell and Pfiffner, *Science*, **100**, 295 (1944).

(3) Ellingson, Henry and McDonald, THIS JOURNAL, **67**, 1711 (1945).

(4) Weijlard, Tishler and Erickson, *ibid.*, **67**, 802 (1945).

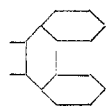
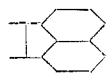
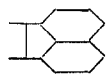
(5) Kuhn and Cook, *Ber.*, **70**, 761 (1937).

(6) Ganapti, *J. Indian Chem. Soc.*, **14**, 627 (1937).

(7) Totter, *J. Biol. Chem.*, **154**, 105 (1944).

(8) Bogert and Davidson, THIS JOURNAL, **55**, 1668 (1933).

TABLE I

| Cpd. | Structure | Ref. | Starting materials Pyrimidine | —C=O / —C=O | Solvent for recryst. | Ultraviolet absorption spectra Maxima mμ | log E | Minima mμ | log E |
|---|---|---|---|---|---|---|---|---|---|
| 1 | II, R = R = H | 4, 5 | A[a] | Glyoxal | Water | 255 | 4.09 | 295 | 2.95 |
| | | | | | | 360 | 3.66 | | |
| 2 | III, R = R = H | | B[b] | Glyoxal | Formic acid–water | 255 | 4.20 | 290 | 2.97 |
| | | | | | | 358 | 3.82 | | |
| 3 | II, R = R = $CH_3$ | 4, 5 | A | Biacetyl | Hydrochloric acid | 245 | 4.13 | 290 | 2.46 |
| | | | | | | 355 | 3.84 | | |
| 4 | III, R = R = $CH_3$ | | B | Biacetyl | Hydrochloric acid | 250 | 4.34 | 295 | 2.92 |
| | | | | | | 355 | 3.94 | | |
| 5 | II, R = R =  | 4, 6 | A | Benzil | Nitromethane | 280 | 4.28 | 255 | 4.16 |
| | | | | | | 385 | 4.01 | 330 | 3.53 |
| 6 | III, R = R =  | | B | Benzil | Dimethylformamide | 270 | 4.32 | 250 | 4.24 |
| | | | | | | 380 | 4.11 | 330 | 3.50 |
| 7 | II, R— = R—  | 5 | A | Phenanthrenequinone | Dimethylformamide | 260 | 4.55 | 280 | 3.97 |
| | | | | | | 290 | 4.18 | 340 | 3.19 |
| | | | | | | 395 | 3.87 | | |
| 8 | III, R— = R—  | | B | Phenanthrenequinone | 0.2 *N* Sodium hydroxide | 263 | 4.69 | 280 | 4.39 |
| | | | | | | 295 | 4.41 | 340 | 3.46 |
| | | | | | | 420 | 4.14 | | |
| 9 | II, R— = R—  | | A | Acenaphthenequinone | Dimethylformamide | 230 | 4.64 | 280 | 3.98 |
| | | | | | | 340 | 4.31 | 370 | 3.84 |
| | | | | | | 385 | 3.88 | | |
| 10 | III, R— = R—  | | B | Acenaphthenequinone | Formic acid–water | 230 | 4.71 | 280 | 4.09 |
| | | | | | | 340 | 4.42 | 373 | 4.05 |
| | | | | | | 385 | 4.08 | | |
| 11 | Pyrimidine A | | .. | ..... | ..... | 285 | 3.76 | 258 | 3.44 |
| 12 | Pyrimidine B | | .. | ..... | ..... | shoulder at 260 | 3.45 | | |

[a] Pyrimidine A is 5,6-diamino-2,4-dihydroxypyrimidine. Pyrimidine B is 4-hydroxy-2,5,6-triaminopyrimidine.

with absolute ethanol and dissolved in 1 liter of water. Glacial acetic acid was added until the solution was neutral to litmus. Dissolving the sodium salt in water and subsequently neutralizing the solution assured the cyclization of cyanoacetylurea to 6-amino-2,4-dihydroxypyrimidine. Additional glacial acetic acid (170 ml., 2.6 moles) was added. A solution of 150 g. (2.18 moles) of sodium nitrite in 400 ml. of water was added slowly with thorough stirring. An immediate precipitation of the bright rose 6-amino-2,4-dihydroxy-5-nitrosopyrimidine took place. Efficient mechanical stirring was continued while sodium hydrosulfite was added slowly with gentle heating until the deep rose color disappeared. This required approximately 1 kg. (5.6 moles). Heating was continued for fifteen minutes after the addition of the last of the sodium hydrosulfite and the mixture was allowed to cool. The yellow 5,6-diamino-2,4-dihydroxypyrimidine bisulfite was filtered with suction and washed well with water. It was transformed to the free pyrimidine for condensation with a dicarbonyl compound.

**5,6-Diamino-2,4-dihydroxypyrimidine.**—The bisulfite salt as prepared above was dissolved in the minimum amount of 10% sodium hydroxide. Ethanol (95%) was then added until the precipitation of the sodium salt of 5,6-diamino-2,4-dihydroxypyrimidine was complete. This product was filtered with suction, washed well with 95% ethanol and dissolved in 600 ml. of water. The aqueous solution was heated to boiling, treated with decolorizing charcoal and filtered. Neutralization of the filtrate to *p*H 7 with hydrochloric acid caused the separation of orange-yellow crystals of 5,6-diamino-2,4-dihydroxypyrimidine. The product, after filtering, washing with water followed by 95% ethanol, and drying, weighed 165 g. (58%). The free pyrimidine base is oxidized readily on standing in contact with air to resinous products insoluble in acid or base. For reaction with dicarbonyl compounds, the material is used as soon as possible after preparation. The bisulfite salt appears to be considerably more stable.

**2,4-Dihydroxypyrimido[4,5-b]pyrazine (Lumazine).**—It was found that condensation in acid solution gave the same yield of a crude product considerably lighter in color than that obtained by condensation in alkaline solution as reported by Weijlard, Tishler and Erickson.[4] To a solution of 8 g. of 5,6-diamino-2,4-dihydroxypyrimidine in 150 ml. of 2 *N* hydrochloric acid was added a solution of 18 g. of glyoxal sodium bisulfite in 200 ml. of water and the mixture boiled for one hour. The deep red solution was cooled to 0.° and sufficient concentrated ammonium hydroxide added to change the *p*H to 10. After standing overnight, the orange-yellow solid was collected by filtration, washed well with 95% ethanol and dried in air. The air-dried material, containing 12% water, weighed 9.6 g. (87%). After crystallization from water and drying at 100° (1 mm.) the product melted at 345–346° (uncor.) in good agreement with the value reported.

**2,4-Dihydroxy-6,7-dimethylpyrimido[4,5-b]pyrazine (6,7-Dimethyllumazine).**—This compound was prepared according to the method of Weijlard, Tishler and Erickson.[4]

*Anal.* Calcd. for $C_8H_8O_2N_4$: C, 49.97; H, 4.20; N, 29.16. Found: C, 49.67; H, 3.97; N, 29.39.

**2,4-Dihydroxy-6,7-diphenylpyrimido[4,5-b]pyrazine (6,7-Diphenyllumazine)** was prepared according to the method of Weijlard, Tishler and Erickson.[4]

*Anal.* Calcd. for $C_{18}H_{12}O_2N_4$: C, 68.34; H, 3.82; N, 17.72. Found: C, 68.16; H, 3.83; N, 17.84.

**2,4-Dihydroxyphenanthro[9,10-e]pyrimido[4,5-b]pyrazine.**[5]—A solution of 2 g. (0.014 mole) of 5,6-diamino-2,4-dihydroxypyrimidine in 40 ml. of water containing 10 ml. of concentrated ammonium hydroxide was added to a solution of 2 g. (0.0096 mole) of phenanthrenequinone in 200 ml. of absolute ethanol. The resulting deep red solution was refluxed for two hours when the deep red color had disappeared and a light orange solid had separated. The mixture was cooled to 0° and the orange-yellow solid was filtered and washed with acetone. Recrystallization from dimethylformamide gave 2.3 g. (76.5%) of yellow crystals in the form of elongated rods exhibiting parallel extinction.

*Anal.* Calcd. for $C_{18}H_{10}O_2N_4$: C, 68.78; H, 3.21; N, 17.83. Found: C, 69.08; H, 3.57; N, 17.81.

**2,4-Dihydroxyacenaphtho[1,2-e]pyrimido[4,5-b]pyrazine).**—A solution of 2 g. (0.011 mole) of acenaphthenequinone dissolved in 30 ml. of hot dimethylformamide was added to a solution of 2 g. (0.014 mole) of 4,5-diamino-2,6-dihydroxypyrimidine dissolved in 100 ml. of 2 *N* hydrochloric acid and the mixture refluxed for three hours. At the end of this time a voluminous pink solid had separated from the reaction mixture. The solvent was removed by distillation under reduced pressure, and the dry pink residue extracted several times with hot acetone to remove unreacted acenaphthenequinone. The light red solid was dissolved in 100 cc. of 2 *N* sodium hydroxide, treated with decolorizing charcoal, and filtered. Acidification of the filtrate to *p*H 5 and cooling to 0° precipitated 2.6 g. (83.5%) of light yellow microcrystalline product.

*Anal.* Calcd. for $C_{16}H_8O_2N_4$: C, 66.66; H, 2.80; N, 19.44. Found: C, 66.85; H, 2.99; N, 19.57.

**4-Hydroxy-2,5,6-triaminopyrimidine Bisulfite.**—The procedure used was essentially that of Totter.[7] However, as was the case with 5,6-diamino-2,4-dihydroxypyrimidine bisulfite, our procedure resulted in a better yield with fewer isolations of intermediates.

A solution of sodium ethoxide was prepared by dissolving 35 g. (1.52 moles) of sodium in 1500 ml. of absolute ethanol. To this was added 100 g. (1.05 moles) of guanidine hydrochloride and 135 g. (1.20 moles) of ethyl cyanoacetate. The mixture was refluxed for three hours and then transferred to a 4-liter beaker. One liter of water was added to dissolve the solid material present. The solution was acidified with 100 ml. of concentrated hydrochloric acid. The resulting 2,6-diamino-4-hydroxypyrimidine present in solution was nitrosated by slow addition with stirring of 100 g. (1.18 moles) of sodium nitrite dissolved in 300 ml. of water. After heating to boiling, the mixture was allowed to cool. The bright rose 5-nitroso derivative was collected by filtration and washed well with water. This material was suspended in 1500 ml. of water in a 4-liter beaker, 80 ml. of 20% sodium hydroxide solution added and the mixture heated to 70–80°, which resulted in partial solution. Reduction of the nitroso group to the amino group was effected by the addition of 500 g. (2.8 moles) of sodium hydrosulfite over a period of fifteen minutes with vigorous mechanical stirring. Heating and stirring were continued for thirty minutes after the last of the sodium hydrosulfite had been added. The rose color originally present was almost completely discharged by this treatment, indicating that the reduction was essentially complete. The solution was heated to boiling and filtered through a jacketed Büchner funnel heated with steam. During this filtration, care was taken to avoid pressures less than 40 cm. otherwise the crystallizing solid stopped the filtration. The light yellow product crystallized immediately. After cooling to 0–10°, the mixture was filtered and the solid washed with cold water. After drying, it weighed 204 g. (87%). Although sufficiently pure for most purposes, it may be purified by crystallization in good yield from a solution of the solid in two parts of water. A portion was crystallized from five parts of water for measurement of the ultraviolet absorption spectrum.

**2-Amino-4-hydroxypyrimido[4,5-b]pyrazine.**—A solution of 15 g. (0.057 mole) of glyoxal sodium bisulfite in 50 ml. of hot water was added with stirring to a solution of 10 g. (0.045 mole) of 4-hydroxy-2,5,6-triaminopyrimidine bisulfite in 50 ml. of hot water. The resulting clear yellow solution soon began depositing a light yellow solid which increased in amount when the mixture was heated for two hours on the steam-bath. After cooling, the solid was collected by filtration, washed with water and dried. The yield was 4.0 g. (54%). A portion was twice recrystallized by dissolving in boiling formic acid, adding water to incipient precipitation and then chilling. The product separated as light yellow microcrystals.

*Anal.* Calcd. for $C_6H_5ON_4$: C, 44.17; H, 3.09; N, 42.93. Found: C, 44.11; H, 3.13; N, 42.61.

**2-Amino-6,7-dimethyl-4-hydroxypyrimido[4,5-b]pyrazine.**—To a solution of 10 g. (0.045 mole) of 4-hydroxy-2,5,6-triaminopyrimidine bisulfite in 50 ml. of hot water was added 10 g. (0.116 mole) of biacetyl. The condensation product began to separate at once, but to ensure complete reaction the mixture was heated on the steam-bath for two hours. After cooling, the solid material was collected by filtration and washed with water followed by 95% ethanol. The dried product weighed 6.2 g. (72%). Recrystallization from 0.5 *N* hydrochloric acid gave light yellow microcrystalline rods exhibiting parallel extinction.

*Anal.* Calcd. for $C_8H_9ON_5$: C, 50.25; H, 4.74; N, 36.63. Found: C, 50.03; H, 4.70; N, 36.30.

**2-Amino-6,7-diphenyl-4-hydroxypyrimido[4,5-b]pyrazine.**—To a solution of 5 g. (0.0225 mole) of 4-hydroxy-2,5,6-triaminopyrimidine bisulfite in 50 ml. of hot water was added a hot solution of 5 g. (0.024 mole) of benzil in a mixture of 50 ml. of ethyl methyl ketone and 50 ml. of 95% ethanol. The resulting mixture was a clear yellow solution which rapidly turned red and began to deposit a yellow solid. After refluxing for three hours, the mixture was filtered while still hot and the solid washed with water followed by acetone. The product weighed 3.8 g. (54%). It was recrystallized from dimethylformamide and washed with alcohol to remove the solvent, giving a microcrystalline yellow solid.

*Anal.* Calcd. for $C_{12}H_{13}ON_5$: C, 68.56; H, 4.15; N, 22.22. Found: C, 68.72; H, 4.21; N, 22.26.

**2-Amino-4-hydroxyphenanthro[9,10-e]pyrimido[4,5-b]-pyrazine.**—Four grams (0.018 mole) of finely powdered 4-hydroxy-2,5,6-triaminopyrimidine bisulfite was added to a solution of 2.0 g. (0.0092 mole) of phenanthrenequinone in 600 ml. of absolute ethanol. The mixture was heated four hours on a steam-bath, when the greenish solid initially formed had become brown and the volume was reduced to approximately 200 ml. Fifty ml. of water was added and the *p*H of the mixture adjusted to 9–10 with 10% sodium hydroxide. The resulting mixture was boiled for fifteen minutes, cooled and filtered. The brown solid was boiled for one-half hour with 6 liters of 1 *N* sodium hydroxide and filtered while hot. The filtrate was adjusted to *p*H 6 with concentrated hydrochloric acid and cooled. The solid product collected by filtration weighed 1.7 g. (59%). After two recrystallizations from 0.2 *N* sodium hydroxide and washing with water followed by acetone, the product was obtained as a bright yellow, microcrystalline solid.

*Anal.* Calcd. for $C_{18}H_{11}ON_5$: C, 69.00; H, 3.54; N, 22.36. Found: C, 68.82; H, 3.70; N, 22.09.

**2-Amino-4-hydroxyacenaphtho[1,2-e]pyrimido[4,5-b]-pyrazine.**—A solution of 1.5 g. (0.0082 mole) of acenaphthenequinone in 30 ml. of hot dimethylformamide was added to a solution of 4.0 g. (0.018 mole) of 4-hydroxy-2,5,6-triaminopyrimidine bisulfite in 40 ml. of hot water. The resulting mixture was boiled gently for one hour, when a yellow solid had precipitated. The solid was collected by filtration while hot and washed with hot water. The dried product weighed 1.4 g. (62%). After two recrystallizations by dissolving in hot formic acid, adding water to incipient precipitation and cooling, the product was obtained in the form of a bright yellow, microcrystalline solid.

*Anal.* Calcd. for $C_{16}H_9ON_5$: C, 66.89; H, 3.16; N, 24.38. Found: C, 67.26; H, 3.22; N, 24.36.

## Summary

1. Procedures have been developed for the synthesis of 5,6-diamino-2,4-dihydroxypyrimidine and 4-hydroxy-2,5,6-triaminopyrimidine bisulfite in appreciably better yields and involving fewer isolations of intermediate products than previously reported.

2. These compounds have been condensed with several dicarbonyl compounds to yield pyrimido[4,5-b]pyrazines symmetrically substituted in the 6- and 7- positions.

3. Ultraviolet absorption spectra of alkaline solutions of the compounds have been measured.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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY AND MICROBIOLOGY, RESEARCH DIVISION, CIBA PHARMACEUTICAL PRODUCTS, INC.]

# Heterocyclic Amines with Antihistaminic Activity[1]

BY CHARLES P. HUTTRER,[1a] CARL DJERASSI, WARREN L. BEEARS,[1b] RUDOLF L. MAYER AND CAESAR R. SCHOLZ

Extensive work from Fourneau's Laboratory[2] has indicated that some relatively simple aminoethers (type F929, F1379, F1464)[3] and diamines (type F1571, F1691, F1709, R. P. 2339, R. P. 2325)[4] possessed antihistaminic activity. Since tertiary amines of this group containing heterocyclic radicals had so far not been studied, we have synthesized a number of asymmetrically-substituted ethylenediamines of the general type $R'-N(R''')-CH_2-CH_2-N<$, in which at least one, and sometimes two, substituents were of an heterocyclic nature (pyridine or pyrimidine series). One member of this series, R. P. 2786, N,N-dimethyl-N'-(*p*-methoxybenzyl)-N'-(α-pyridyl)-ethylenediamine, has since been described.[4a]

The work reported here was not published earlier pending extensive pharmacological and clinical investigation.[5] In recent articles, Whitmore and co-workers[6] have described secondary amines of similar structure as part of their work on antimalarials.

The secondary amines (Table I) were prepared by condensing the primary amines with a dialkylaminoethyl halide in toluene solution in the presence of sodium or lithium amide (procedure A). This method, first introduced by Tschitschibabin,[7] has been used recently by Eisleb[8] and by Whitmore.[6] We usually preferred this method to that of condensing the asymmetrically-substituted diamine with an halogen-substituted heterocyclic compound (procedure B), because of the latter's lower degree of reactivity and higher cost.

A $R'NH + XCH_2CH_2N<$ → $R'NHCH_2CH_2N<$

B $R'X + H_2NCH_2CH_2N<$ → $R'NHCH_2CH_2N<$

R' = heterocyclic

In procedure A, the best yields were obtained with a substantial excess of the primary amine and a slight excess of sodamide. In the cases where the alkyl side chain was a dimethyl or diethylaminoethyl group, we employed the hydrochloride or hydrobromide salts. These salts were much easier to handle than the free halides, but necessitated the use of double quantities of sodamide or lithium amide. Whitmore, *et al.*,[6] employed the free halides, but that method is applicable to dimethylaminoethyl halides only if special precautions are taken. Knorr[9] reported that the dimethyl derivative polymerized very rapidly to the cyclic dimer. Recent kinetic studies from our laboratories have indicated that this compound can be stored for prolonged periods of time under proper conditions. These results will be reported in the near future.

Tertiary amines (Table II) were prepared either by condensing the dialkylaminoethyl substituted amino heterocyclic compound with an alkyl-, or aralkyl halide (procedure C); by condensing the halogenated heterocyclic substance with an asymmetrically tri-substituted alkylenediamine (procedure D); or by condensing the alkyl or aralkyl substituted amino heterocyclic derivative

(1) Presented on the program of the Division of Medicinal Chemistry at the Atlantic City meeting of the American Chemical Society, April 8–12, 1946.

(1a) Present address: Warner Institute for Therapeutic Research, 113 West 18th St., New York, N. Y.

(1b) Present address: B. F. Goodrich Company, Akron, Ohio.

(2) For key references and pharmacological results, *cf.* Staub, *Ann. Inst. Pasteur*, **63**, 400 (1939), and Halpern, *Arch. Intern. Pharmacodynamie*, **68**, 339 (1942).

(3) F929, 2-isopropyl-5-methylphenoxyethyldiethylamine; F1379, 2-methyl-5-isopropylphenoxyethyldiethylamine; F1464, 2-isopropyl-5-methylphenoxyethylpiperidine.

(4) F1571, N,N-Diethyl-N'-phenyl-N'-ethylethylenediamine; F-1691, N,N-diethyl-N'-(2-methyl-5-isopropylphenyl)-ethylenediamine; F1709, N,N-diethyl-N'-phenyl-N'-isopropylethylenediamine; R. P. 2339, N,N-dimethyl-N'-benzyl-N'-phenyl ethylenediamine; R. P. 2325, N,N-dimethyl N'-ethyl-N'-phenylethylenediamine.

(4a) Bovet, Horclois and Walthert, *Compt. rend. soc. biol.*, **138**, 99 (1944); C. A., **39**, 3070 (1945).

(5) (a) Mayer, Huttrer and Scholz, *Science*, **102**, 93 (1945); *Feder. Proc.*, **4**, 129 (1945); (b) Rennick, Chess, Hays, Mathieson, Mayer and Yonkman, *ibid.*, 4, 133 (1945); (c) Yonkman, Chess, Mathieson and Hansen, *ibid.*, **4**, 143–144 (1945); (d) Mayer, *J. Allergy*, **17**, 153 (1946); (e) Koepf, Arbesman and Lenzner, *Feder. Proc.*, **5**, 56 (1946).

(6) *Cf.* (a) Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945); (b) D. P. J. Goldsmith, Ph.D. Thesis, Penn State College, 1942; (c) Adams and Whitmore, THIS JOURNAL, **67**, 735 (1945).

(7) Tschitschibabin, Konowalowa and Konowalowa, *Ber.*, **54**, 814 (1921).

(8) Eisleb, *ibid.*, **74**, 1433 (1941).

(9) Knorr, *Ber.*, **37**, 3507 (1904).