[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW MEXICO HIGHLANDS UNIVERSITY]

Potential Purine Antagonists. XII. Synthesis of 1-Alkyl(aryl)-4,6-disubstituted Pyrazolo[3,4-*d*]pyrimidines[1]

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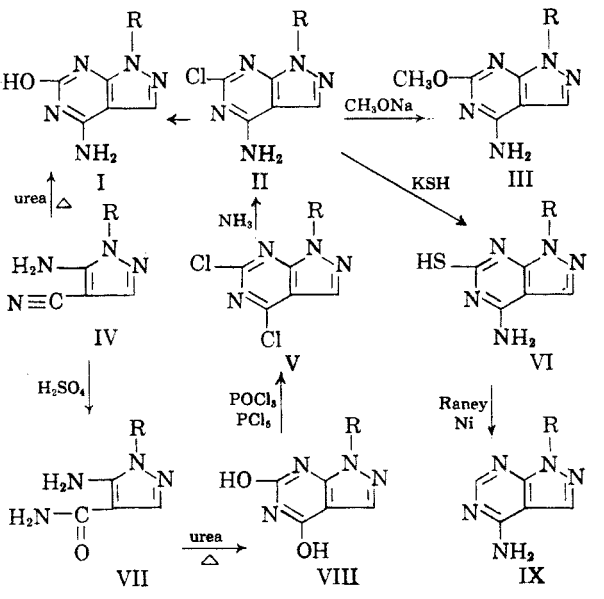
Various 1-alkyl(aryl)-4,6-disubstituted pyrazolo[3,4-*d*]pyrimidines were prepared *via* the corresponding 1-alkyl(aryl)-5-amino-4-cyanopyrazoles (IV). The urea fusion of the 1-alkyl(aryl)-5-aminopyrazole-4-carboxamide (VII) prepared from IV yielded the corresponding 1-alkyl(aryl)-4,6-dihydroxypyrazolo[3,4-*d*]pyrimidine (VIII) which was treated with phosphorus oxychloride and phosphorus pentachloride to yield the 4,6-dichloropyrazolo[3,4-*d*]pyrimidine (V). The replacement of the chlorine atoms of V was investigated and the position of substitution determined.

The report of the activity possessed by certain 1-methyl-4-substituted aminopyrazolo[3,4-*d*]pyrimidines and 4-hydroxy-6-aminopyrazolo[3,4-*d*]pyrimidine in the inhibition of the growth of certain experimental neoplasms *in vivo*[3] suggested further synthetic work be carried out in this series. This report is concerned with the preparation of certain 1-alkyl(aryl)-4,6-disubstituted pyrazolo[3,4-*d*]pyrimidines.

As previously described the general synthetic route to the pyrazolo[3,4-*d*]pyrimidines devised in this laboratory begins with a 5-amino-4-cyanopyrazole.[4-7] Hoggarth and Paget[8] have recently reported the preparation of 6-amino-4-methyl-pyrazolo(3,4-*d*)pyrimidine from the condensation of hydrazine and 4-alkylthiopyrimidines.

While the present investigation was in process, Schmidt and Druey[9] reported a synthesis of several pyrazolo[3,4-*d*]pyrimidines from 3-aminopyrazole-4-carboxylate in a manner similar to that utilized by Robins[4] who employed 3-aminopyrazole-4-carboxamide as a pyrazole intermediate. Schmidt and Druey[9] list 4,6-dihydroxy-1-phenylpyrazolo-[3,4-*d*]pyrimidine (III, R = C_6H_5) in a table and record the melting point as 297–298°. No experimental directions were reported for this preparation. This compound was prepared in our laboratory by the urea fusion of 5-amino-1-phenylpyrazole-4-carboxamide (VII, R = C_6H_5)[5] and found to possess a melting point of 372–373°. In a similar manner a number of 1-alkyl(aryl)-4,6-dihydroxypyrazolo-[3,4-*d*]pyrimidines (VIII) were prepared by heating the corresponding 1-alkyl(aryl)-4-aminopyrazole-

REACTION SCHEME I



carboxamides (VII)[5] with urea. In general the yields were good, and the crude 4,6-dihydroxypyrazolo[3,4-*d*]pyrimidine was utilized directly for further synthetic work. Fusion of a substituted urea such as *N*-methylurea or *N*-phenylurea with 4 - amino - 1 - methylpyrazole - 5 - carboxamide (VII, R = CH_3) gave 4,6-dihydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine (VIII, R = CH_3) instead of a 1-methylpyrazolo[3,4-*d*]pyrimidine substituted at nitrogen "5" or "7". Chlorination of VIII with phosphorus oxychloride in the presence of an excess of phosphorus pentachloride gave the corresponding 1-alkyl(aryl)-4,6-dichloropyrazolo[3,4-*d*]pyrimidine (V) in good yield. It is interesting to note that with V when R = H, these conditions for chlorination were unsuccessful, and special reaction conditions have previously[6] been found necessary for the preparation of 4,6-dichloropyrazolo[3,4-*d*]pyrimidine.

Treatment of V, R = CH_3, in 1*N* potassium hydroxide gave 6-chloro-4-hydroxy-1-methylpyrazolo-[3,4-*d*]pyrimidine (XI). Increased strength of the

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(3) Skipper, Robins, Thomson, Cheng, Brockman, and Schabel, *Cancer Research*, **17**, 579 (1957).

(4) Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

(5) Cheng and Robins, *J. Org. Chem.*, **21**, 1240 (1956).

(6) Robins, *J. Am. Chem. Soc.*, **79**, 6407 (1957).

(7) Cheng and Robins, *J. Org. Chem.*, **23**, 191 (1958).

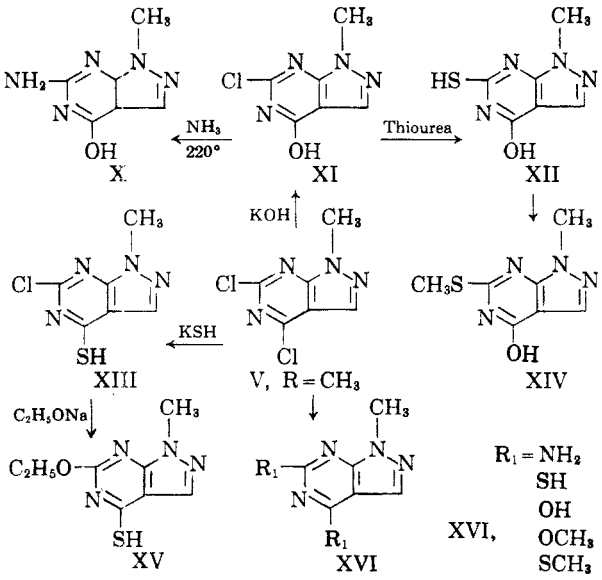
(8) Hoggarth and Paget, Brit. Patent, **716,327** [*Chem. Abstr.*, **49**, 5178a (1955)].

(9) Schmidt and Druey, *Helv. Chim. Acta*, **39**, 986 (1956).

base and longer reaction time did not hydrolyze the chlorine atom in position "6." Treatment of V, R = CH_3, with refluxing concentrated hydrochloric acid, however, readily gave the original dihydroxy derivative, VIII, R = CH_3. The selection replacement of the chlorine atoms in the 1-alkyl(aryl)-4,6-dichloropyrazolo[3,4-*d*]pyrimidines (V) was rather extensively investigated. As with 4,6-dichloropyrazolo[3,4-*d*]pyrimidine[6] selective nucleophilic replacement of the "4" chloro atom could be accomplished under relatively mild conditions. It would appear that the "4" chloro atom of V is more susceptible to nucleophilic replacement than the chlorine atom of the corresponding 1-alkyl(aryl)-4-chloropyrazolo[3,4-*d*]pyrimidine.[5] Thus, V, R = CH_3, reacted with alcoholic ammonia heated on the steam bath (70°) to give 4-amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (II, R = CH_3) while 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine required heating in a bomb[5] with the same reagent to effect replacement of the chlorine atom in position "4."

The diamino derivative, XVI, $R_1 = NH_2$, was obtained from V, R = CH_3, and alcoholic ammonia heated to 180° in a bomb.

REACTION SCHEME II

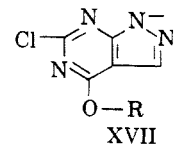


The structure of II, R = CH_3, was determined in the following manner. When II, R = CH_3, was refluxed with concentrated hydrochloric acid, 4-amino-6-hydroxy-1-methyl-pyrazolo[3,4-*d*]pyrimidine (I, R = CH_3) was formed in good yield. I, R = CH_3, was also synthesized by the fusion of urea and 5-amino-4-cyano-1-methylpyrazole (IV, R = CH_3).

Further proof of the structure assigned II, R = CH_3, was obtained as follows: 4-Amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (II, R = CH_3) was treated with 3 *N* potassium hydrosulfide in a bomb at 110° to give 4-amino-6-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine (VI, R = CH_3). Raney Nickel dethiation converted VI, R = CH_3, to 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine (IX), which had been previously prepared[5] from 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine.

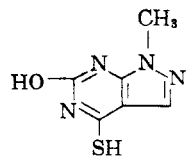
In general, the replacement of the second chlorine atom at position "6" was more difficult and required a higher temperature. Occasionally, however, the replacement of both chlorine atoms took place simultaneously. For example, the isolation of 6-chloro-4-dimethylamino-1-methylpyrazolo[3,4-*d*]pyrimidine and 6-chloro-4-(*p*-chloroanilino)-1-methylpyrazolo[3,4-*d*]pyrimidine under various experimental conditions was unsuccessful. In these two instances the 4,6-bis-substituted-amino derivatives were obtained exclusively.

1-Alkyl(aryl)-4,6-dialkoxypyrazolo[3,4-*d*]pyrimidines were prepared from V, R = CH_3, and sodium alkoxides. It is interesting to note that in the case of 4,6-dichloropyrazolo[3,4-*d*]pyrimidine[6] a monosubstituted alkoxy derivative was obtained under carefully controlled conditions; but when the 1-position was substituted with an alkyl or aryl group, a disubstituted alkoxy derivative was obtained exclusively. This might possibly be explained in structure XVII by the acquisition of a negative charge by nitrogen at position "1" in the basic medium. Thus, the increase of electron density of the ring could hinder the nucleophilic displacement of the second chlorine atom. This type of deactivation would not be possible if position "1" were substituted with an alkyl or aryl group. The preparation of 4,6-dimercapto-1-methylpyrazolo(3,4-*d*)pyrimidine (XVI, R_1 = SH) proceeded smoothly from V, R = CH_3, and thiourea in refluxing ethanol. Sodium methylmercaptide and V, R = CH_3, gave 1-methyl-4,6-bis(methylthio)-pyrazolo[3,4-*d*]pyrimidine (XVI, $R_1 = SCH_3$).



XVII

When 4,6-dihydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine (VIII, R = CH_3) was treated with phosphorus pentasulfide in pyridine, 6-hydroxy-4-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine (XVIII) was obtained.



XVIII

The structure of XVIII was established since the isomer, 4-hydroxy-6-mercapto-1-methylpyrazolo-[3,4-*d*]pyrimidine (XII) was prepared from 5-amino-1-methylpyrazolo[3,4-*d*]pyrimidine-4-carboxamide (VII, R = CH_3) fused with thiourea.

Treatment of XI and thiourea in refluxing ethanol also gave XII, thus providing proof of the structure previously assigned XI. Careful methylation of XII with dimethylsulfate gave 4-hydroxy-1-methyl-6-methylthiopyrazolo[3,4-*d*]pyrimidine (XIV).

When 6-chloro-4-hydroxy-1-methylpyrazolo[3,-4-*d*]pyrimidine (XI) was treated with alcoholic ammonia at 220°, 6-amino-4-hydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine (X) was obtained. Careful treatment of V, R = CH_3, with potassium hydrosulfide gave 6-chloro-4-mercapto-1-methylpyrazolo-[3,4-*d*]pyrimidine (XIII). The compound, XIII, was further treated with sodium ethoxide to yield 6-ethoxy-4-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine (XV). This type of selective replacement of the chlorine atoms is further illustrated by the reaction of II, R = CH_3, and sodium methoxide to give 4-amino-6-methoxy-1-methylpyrazolo[3,4-*d*]-pyrimidine (III).

Similarly, V, R = CH_3, and sodium ethylmercaptide at room temperature gave 6-chloro-4-ethylthio - 1 - methylpyrazolo[3,4-*d*]pyrimidine (XIX) which in turn when treated with sodium ethoxide yielded XX.

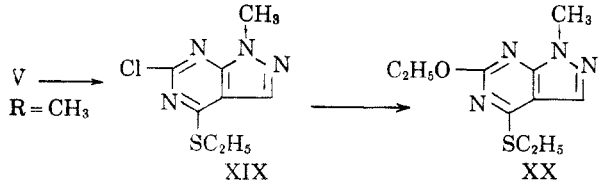


Table II lists the 1-alkyl(aryl)-6-chloro-4-(substituted amino)pyrazolo[3,4-*d*]pyrimidines prepared from V. Table III lists the 1-alkyl(aryl)-4,6-bis-(substituted amino)pyrazolo[3,4-*d*]pyrimidines prepared from V and the corresponding primary or secondary amines. By careful study of the reaction time and solvent, it was possible in most cases to effect mono- or disubstitution as desired. Table I lists a number of 1-alkyl(aryl)-4,6-disubstituted pyrazolo[3,4-*d*]pyrimidines which have been prepared in this study.

EXPERIMENTAL[10]

Preparation of 4,6-dihydroxy-1-methylpyrazolo[3,4-d]pyrimidine (VII, R = CH_3). *Method 1.* Fifty grams of 5-amino-1-methylpyrazolo-4-carboxamide[5] was fused with 100 g. of urea at 180–200° for 1 hr. The mixture melted in the beginning of the fusion; it then became mushy; finally, with continuous agitation, the reaction mixture solidified. The cooled solid mass was dissolved in 1 l. of hot, dilute potassium hydroxide. The solution was treated with charcoal and filtered. The boiling filtrate was acidified with glacial acetic acid. A white precipitate formed which was filtered and dried at 130° for 5 hr. to give 55 g. (93%) of white powder, m.p. >300°. This crude product was employed directly for chlorination to give 4,6-dichloro-1-methylpyrazolo[3,4-*d*]-pyrimidine (IV, R = CH_3). Ultraviolet absorption spectra showed this product to be above 90% pure. An analytically pure sample was obtained only by acid hydrolysis of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine (V, R = CH_3) as indicated in Method 2.

Method 2. Acid hydrolysis of 4,6-dichloro-1-methylpyrazolo[3,4-d]pyrimidine (V, R = CH_3). Four grams of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine was suspended in 15 ml. of water. To this suspension was added 80 ml. of concentrated hydrochloric acid. The mixture was refluxed for 18 hr. A white precipitate resulted on cooling. The product was filtered and reprecipitated once from dilute alkaline solution by acetic acid to give white needles, m.p. >300°. The yield of pure 4,6-dihydroxy-1-methylpyrazolo[3,4-*d*]-pyrimidine (III, R = CH_3) was 2 g. (65%).

Anal. Calcd. for $C_6H_6N_4O_2$: C, 43.4; H, 3.6; N, 33.7. Found: C, 43.3; H, 3.6; N, 33.7.

Preparation of 4,6-dihydroxy-1-phenylpyrazolo[3,4-d]pyrimidine (VIII, R = C_6H_5). Fifty grams of 5-amino-1-phenylpyrazole-4-carboxamide[5] was fused with 100 g. of urea at approximately 200° until the fused mass solidified. The cooled melt was dissolved in dilute sodium hydroxide; the solution was treated with charcoal and filtered. The hot filtrate was acidified with glacial acetic acid and the white precipitate collected. The solid was washed with water and dried at 130° to yield 53 g. (94%) of white powder, m.p. >300°. A small amount of the product was recrystallized from 80% acetic acid to give long, white needles, m.p. 320–321° (copper block).

Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.9; H, 3.5; N, 24.6. Found: C, 58.1; H, 3.6; N, 24.6.

Preparation of 4,6-dichloro-1-methylpyrazolo[3,4-d]pyrimidine (V, R = CH_3). One hundred grams of finely powdered 4,6-dihydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine was mixed with 200 ml. of phosphorus oxychloride and 700 g. of phosphorus pentachloride. The mixture was refluxed for 28 hr. and the excess phosphorus oxychloride distilled at reduced pressure using a steam bath as a source of heat. The sirupy residue was poured, with vigorous stirring, onto 2 kg. of crushed ice. The cold, aqueous suspension was filtered and the filtrate extracted with chloroform. The chloroform extract, after being washed well with ice water until free of acid, was dried over anhydrous magnesium sulfate. The solvent was then distilled, and the residue solidified on cooling to yield 61 g. (50%) of tan solid, m.p. 82–85°. The product was recrystallized from absolute ethanol followed by a second recrystallization from heptane to give white needles, m.p. 87–88°.

Anal. Calcd. for $C_6H_4N_4Cl_2$: C, 35.5; H, 2.0; N, 27.6. Found: C, 36.0; H, 2.2; N, 27.6.

Preparation of 4,6-dichloro-1-phenylpyrazolo[3,4-d]pyrimidine (V, R = C_6H_5). Forty grams of 4,6-dihydroxy-1-phenylpyrazolo[3,4-*d*]pyrimidine was refluxed with a mixture of 160 g. of phosphorus pentachloride and 500 ml. of phosphorus oxychloride. The solution was refluxed for 2 hr. The excess phosphorus oxychloride was removed and the sirupy residue poured, with vigorous stirring, onto 1 kg. of crushed ice. The solution was extracted with chloroform, and the chloroform extract was washed and dried. A light-yellow solid remained after the distillation of the chloroform to yield 42 g. (90%), m.p. 120–122°. The product was recrystallized from heptane to give white needles, m.p. 126–127°.

Anal. Calcd. for $C_{11}H_6N_4Cl_2$: C, 49.8; H, 2.3; N, 21.1; Cl, 26.8. Found: C, 50.2; H, 2.4; N, 20.8; Cl, 26.6.

Preparation of 1-p-chlorophenyl-4,6-dichloropyrazolo[3,4-d]-pyrimidine. To 300 g. of phosphorus oxychloride and 60 g. of phosphorus pentachloride was added 27 g. of 1-*p*-chlorophenyl-4,6-dihydroxypyrazolo[3,4-*d*]pyrimidine (VIII, R = *p*-C_6H_4Cl). The solution was refluxed for 2.5 hr. and the excess phosphorus oxychloride removed under reduced pressure. The sirupy residue was poured on crushed ice and the solution kept cooled and stirred for 30 min. The precipitate was filtered and repeatedly washed with ice water and finally allowed to dry at room temperature. The crude

(10) All melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus, unless otherwise stated.

yield was 23.4 g., m.p. 140–142°. Recrystallization from *n*-heptane raised the melting point to 146–147°.

Anal. Calcd. for $C_{11}H_5N_4Cl_3$: C, 44.1; H, 1.7. Found: C, 44.4; H, 1.7.

Preparation of 4-amino-6-chloro-1-methylpyrazolo[3,4-d]-pyrimidine (II, R = CH_3). Ten g. of finely powdered 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine was added to 200-ml. of alcoholic ammonia. The mixture was then boiled gently on a steam bath to dryness. Another 200-ml. portion of alcoholic ammonia was added to the dry mass, and the solution was again evaporated to dryness. The residue was washed with cold water and recrystallized from 400 ml. of water to give white needles, m.p. 295–296°. The yield of 4-amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine was 7 g. (78%).

Anal. Calcd. for $C_6H_6N_5Cl$: C, 39.3; H, 3.3; N, 38.2. Found: C, 39.3; H, 3.7; N, 38.6.

Preparation of 6-chloro-4-hydroxy-1-methylpyrazolo[3,4-d]-pyrimidine (IX). Five g. of 4,6-dichloro-1-methylpyrazolo-[3,4-*d*]pyrimidine (V, R = CH_3) was refluxed with 5 g. of potassium hydroxide and 1 g. of activated charcoal in 100 ml. of water for 3 hr. The solution was filtered and the hot filtrate acidified with glacial acetic acid. The precipitate was collected and reprecipitated to give white needles, m.p. 267–268°. The yield of 6-chloro-4-hydroxy-1-methyl-pyrazolo[3,4-*d*]pyrimidine (XI) was 4 g. (88%).

Anal. Calcd. for $C_6H_5N_4OCl$: C, 39.1; H, 2.7; N, 30.4. Found: C, 39.1; H, 3.1; N, 30.7.

Preparation of 4,6-diamino-1-methylpyrazolo[3,4-d]pyrimi-dine (XVI, R = CH_3). Ten g. of 4,6-dichloro-1-methyl-pyrazolo[3,4-*d*]pyrimidine was heated with 120 ml. of alcoholic ammonia in a bomb at 210° for 12 hr. The reaction mixture was evaporated to dryness, and the solid product was washed with a small amount of dilute alkali and then with water. Recrystallization from water gave small, white needles, m.p. >300°. The yield of 4,6-diamino-1-methyl-pyrazolo[3,4-*d*]pyrimidine was 2 g. (25%).

Anal. Calcd. for $C_6H_8N_6$: C, 43.8; H, 4.9. Found: C, 42.8, 44.8; H, 4.4, 5.1.

Preparation of 4,6-diamino-1-phenylpyrazolo[3,4-d]pyrimi-dine. Ten g. of V, R = C_6H_5, was added to 150 ml. of ethanol saturated with dry ammonia at 0°. The mixture was then heated at 190° in a bomb for 12 hr. The solvent was then evaporated and the residue washed with water and recrystal-lized from dilute ethanol to yield 6.3 g. of a white solid, m.p. 236–237°.

Anal. Calcd. for $C_{11}H_{10}N_6$: C, 58.3; H, 4.5; N, 37.5. Found: C, 58.0; H, 4.9; N, 38.0.

Preparation of 4-amino-6-hydroxy-1-methylpyrazolo[3,4-d]-pyrimidine (I, R = CH_3). *Method 1. Hydrolysis of 4-amino-6-chloro-1-methylpyrazolo[3,4-d]pyrimidine* (II, R = CH_3). A mixture of 12 g. of II, R = CH_3, and 100 ml. of concentrated hydrochloric acid was refluxed for 10 hr. All the solid dissolved after 30 min. After 8 hr. of refluxing, the solution was cooled and the product filtered. Purification was accomplished by reprecipitation from a hot, dilute basic solution with glacial acetic acid to give 7 g. (64%) of white powder, m.p. >300°.

Anal. Calcd. for $C_6H_7N_5O_2$: C, 43.6; H, 4.3. Found: C, 43.4; H, 4.3.

Method 2. Fusion of urea and 5-amino-4-cyano-1-methyl-pyrazole (IV, R = CH_3). Twenty g. of IV, R = CH_3, was fused with 40 g. of urea at 200°. The mixture melted and then gradually formed a paste which finally solidified after stirring for 30 min. The crude product was purified by re-precipitation from a basic solution to yield 10.4 g. (34%). The ultraviolet absorption spectra at *p*H 1 and *p*H 11 was identical to that prepared by Method 1.

Preparation of 6-amino-4-hydroxy-1-methylpyrazolo[3,4-d]-pyrimidine (X, R = CH_3). A mixture of 7 g. of 6-chloro-4-hydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine (XI) and 120 ml. of alcoholic ammonia was heated in a bomb at 220° for 12 hr. The reaction product was then evaporated to dryness. The residue was dissolved in dilute hydrochloric acid, the solution filtered, and the product reprecipitated by adding ammonium hydroxide to the hot filtrate to give 4.5 g. (72%) of white powder, m.p. >300°.

Anal. Calcd. for $C_6H_7N_5O$: C, 43.6; H, 4.3; N, 42.4. Found: C, 43.7; H, 4.5; N, 42.5.

Preparation of 6-hydroxy-4-mercapto-1-methylpyrazolo[3,4-d]pyrimidine (X, R = CH_3). A solution of 30 g. of finely powdered 4,6-dihydroxy-1-methylpyrazolo[3,4-*d*]pyrimidine, 150 g. of phosphorus pentasulfide and 600 ml. of dry pyridine was refluxed for 12 hr. The excess pyridine was distilled under reduced pressure from a steam bath. The sirupy residue was heated with 4 l. of water for 5 hr. on the steam bath. The solid product was filtered and recrystallized from water to give 18 g. (55%) of a light-yellow solid, m.p. >310°.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.6; H, 3.3; N, 30.8. Found: C, 40.0; H, 3.3; N, 31.1.

Preparation of 4,6-dimercapto-1-methylpyrazolo[3,4-d]pyrim-idine (XVI, R_1 = SH). Ten g. of powdered 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine and 10 g. of thiourea were added to 150 ml. of absolute ethanol and the solution refluxed for 3 hr. The solid substance, which precipitated from the hot solution, was filtered and reprecipitated from dilute potassium hydroxide by glacial acetic acid to give 7.2 g. (74%) of light-yellow powder, m.p. 292–293°.

Anal. Calcd. for $C_6H_6N_4O_2$: C, 36.4; H, 3.1; N, 28.3. Found: C, 36.6; H, 2.9; N, 28.1.

Preparation of 4,6-dimercapto-1-phenylpyrazolo[3,4-d]py-rimidine. To a solution of 13 g. of thiourea, dissolved in 120 ml. of absolute ethanol, was added 10 g. of V, R = C_6H_5. The solution was refluxed for 4 hr. and then allowed to cool. The filtered product was dissolved in hot, dilute potassium hydroxide and precipitated with acetic acid to give 3.5 g. of product.

Anal. Calcd. for $C_{11}H_8N_4S_2$: C, 50.8; H, 3.1; N, 21.5. Found: C, 51.2; H, 3.3; N, 21.1.

Preparation of 1-alkyl(aryl)-6-chloro-4-substitutedamino-pyrazolo[3,4-d]pyrimidines. See Table II. The preparation of these derivatives can best be illustrated by the following examples:

6-Chloro-4-(o-chloroanilino)-1-methylpyrazolo[3,4-d]pyrimi-dine. Five g. of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimi-dine (V, R = CH_3) was mixed with 13 g. of *o*-chloroaniline in 150 ml. of absolute ethanol. The mixture was evaporated to dryness slowly on a steam bath. The residue was washed with a little cold ethanol and recrystallized from a mixture of 2-ethoxyethanol and water. The yield was 6.2 g. (86%) of small, white plates, m.p. 224–225°.

Anal. Calcd. for $C_{12}H_9N_5Cl_2$: N, 23.7. Found: N, 23.4.

6-Chloro-4-(2',4'-dimethylanilino)-1-methylpyrazolo[3,4-d]-pyrimidine. Five g. of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]-pyrimidine (V, R = CH_3), 10 g. of 2,4-dimethylaniline, and 150 ml. of absolute ethanol were heated on a steam bath for 8 hr. The solution was then evaporated to dryness. The solid mass was washed with a little ether and recrystallized from ethanol to give 4 g. (57%) of white needles, m.p. 241°.

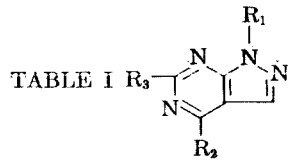
Anal. Calcd. for $C_{14}H_{14}N_5Cl$: C, 58.5; H, 4.9; N, 24.3. Found: C, 58.8; H, 4.7; N, 24.0.

6-Chloro-1-methyl-4-(1',1',3',3'-tetramethylbutylamino)-pyrazolo[3,4-d]pyrimidine. Five g. of 4,6-dichloro-1-methyl-pyrazolo[3,4-*d*]pyrimidine (V, R = CH_3), 15 g. of 1,1,3,3-tetramethylbutylamine, and 150 ml. of absolute ethanol were evaporated to dryness on a steam bath. The crude compound was recrystallized from benzene and ethanol to give 6.5 g. (72%) of white needles, m.p. 183–184°.

Anal. Calcd. for $C_{14}H_{22}N_5Cl$: C, 56.9; H, 7.5; N, 23.6. Found: C, 56.9; H, 7.7; N, 23.1.

6-Chloro-4-β-hydroxyethylamino-1-phenylpyrazolo[3,4-d]-pyrimidine. A mixture of 4,6-dichloro-1-phenylpyrazolo-[3,4-*d*]pyrimidine, 20 g. of ethanolamine, and 100 ml. of 50% methanol was boiled on a steam bath for 3 hr. A white precipitate formed gradually in the hot solution. The mixture was cooled and filtered, and the product was recrystal-

TABLE I



SUBSTITUTED PYRAZOLO[3,4-*d*]PYRIMIDINES

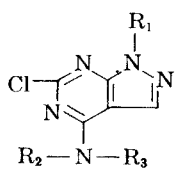
R_1	R_2	R_3	M.P. (°C.)	Yield (%)	U.v. Absorption λ_{max}, mμ pH 11	ε	λ_{max}, mμ Ethanol	ε	Recrystn.[a] Solvents	Analyses, % Calcd. C	H	N	Found C	H	N
CH_3	OH	OH	>300	93.0	247	12,600			E	43.4	3.64	33.7	43.3	3.60	33.7
					269	9,300									
CH_3	Cl	Cl	87–88	43.4			271	6,500	D	35.5	1.97	27.6	36.0	2.19	27.6
CH_3	OH	Cl	267–268	88.0	266	9,240			E	39.1	2.73	30.4	39.0	2.82	30.7
CH_3	OH	SH	>300	73.6	239	8,740			I	39.6	3.32	30.8	39.8	3.86	30.7
					278	11,600									
CH_3	SH	OH	>300	90.0	259	7,100	232	8,200	E	39.6	3.32	30.8	40.0	3.29	31.1
					331	17,100	262	6,550							
							300	6,500							
CH_3	SH	SH	292–293	73.7	240	19,800									
					325	19,800			E	36.4	3.05	28.3	36.6	2.94	28.1
CH_3	SH	Cl	223	45.5	237	16,200			E			27.9			27.1
					326	23,200									
CH_3	NH_2	Cl	295–296	77.5	266	10,500			A	39.3	3.30	38.2	39.3	3.70	38.6
CH_3	NH_2	NH_2	>300	24.8	276	10,200			A	43.8	4.90		42.8	5.12	
CH_3	OH	NH_2	>300	71.9	267	19,300			F	43.6	4.27	42.4	43.7	4.48	42.5
CH_3	NH_2	OH	>300	64.8	247	19,000			E and F	43.6	4.27		43.4	4.34	
					269	13,000									
CH_3	OCH_3	OCH_3	106	43.6	259	7,660			G	49.5	5.15	28.8	49.8	5.29	28.6
CH_3	SCH_3	SCH_3	100.5–101.5	87.8			249	15,800	G	42.5	4.45	24.7	42.2	4.53	24.3
							267	12,600							
							288	13,800							
CH_3	OC_2H_5	OC_2H_5	99–99.5	56.1	259	9,320			B			25.2			25.2
CH_3	SC_2H_5	SC_2H_5	61–62	79.7			242	13,000	C	47.2	5.55		47.0	5.62	
							291	10,200							
CH_3	SCH_3	Cl	144–145	53.8			289	12,400	H	39.3	3.29		39.7	3.51	
CH_3	OH	SCH_3	258–260	25.8	238	19,000									
					271	12,700			C	42.9	4.11	28.6	43.1	4.36	29.0
CH_3	NH_2	OCH_3	285–286	58.0			266	14,000	A	46.8	5.06		46.5	4.81	
CH_3	NH_2	SH	>310	49.4	238	14,800			E	39.8	3.89		39.7	3.82	
					288	23,000									
CH_3	SH	OC_2H_5	240	80.9	231	14,800	256	4,000							
					269	4,400	324	14,500	E	45.6	4.80		45.2	4.50	
					313	16,400									
CH_3	SC_2H_5	Cl	112–113	75.6			291	18,300	B	42.1	3.97		42.4	4.11	
CH_3	SC_2H_5	OC_2H_5	92–93.5	57.6			241	12,600	C	50.5	5.92		51.4	6.06	
							262	10,000							

TABLE I (*Continued*)

R_1	R_2	R_3	M.P. (°C.)	Yield (%)	U.v. Absorption λ_{max}, mμ pH 11	ε	U.v. Absorption λ_{max}, mμ Ethanol	ε	Recrystn.[a] Solvents	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	$OC_6H_4Br(p)$	Cl	152–152.5	59.8			261	22,900	C	42.5	2.40	16.5	42.4	2.49	16.4
CH_3	$OC_6H_4NO_2(p)$	Cl	180–180.5	31.4			271	10,700	C	47.2	2.64		47.3	2.76	
C_6H_5	OH	OH	320	94.0	239	25,300			I	58.0	3.53	24.6	58.1	3.57	24.6
C_6H_5	Cl	Cl	126–127	90.5			249	32,200	D	49.9	2.27	21.1	50.2	2.43	20.8
C_6H_5	OH	Cl	280–281	96.8	233	27,000			E	53.6	2.86	22.7	53.4	2.92	23.2
					275	13,800									
C_6H_5	SH	SH	230–232	35.8	238	24,200			E	50.8	3.10	21.5	51.2	3.25	21.1
					275	11,200									
					326	18,200									
C_6H_5	OCH_3	OCH_3	121–121.5	82.7			241	38,000	G	61.0	4.72	21.8	61.3	5.00	21.6
C_6H_5	OC_2H_5	OC_2H_5	93	70.6			222	23,800	B	60.1	5.37	18.7	60.5	5.39	18.7
							251	21,200							
							282	18,600							
C_6H_5	$OC_6H_4Br(p)$	Cl	128–129	33.0			240	34,000	B	50.9	2.52		50.7	2.74	
C_6H_5	NH_2	NH_2	236–237	73.9	274	13,500			C	58.3	4.45	37.5	58.0	4.62	37.6
p-ClC_6H_4	OH	OH	>300	73.0	242	19,800			E	50.3	2.68	21.4	50.7	2.40	21.6
					264	11,200									
p-ClC_6H_4	Cl	Cl	146–147	74.2			254	36,200	L	44.1	1.68		44.4	1.65	
p-ClC_6H_4	NH_2	OH	>300	33.3	246	22,200			E			26.8			26.8

[a] Recrystallization solvents: A, water; B, ethanol; C, ethanol and water; D, heptane; E, reprecipitated from dilute potassium hydroxide with acetic acid; F, reprecipitated from hydrochloric acid with ammonium hydroxide; G, methanol; H, toluene; I, acetic acid; L, benzene and heptane.

TABLE II



SUBSTITUTED 4-AMINO-6-CHLOROPYRAZOLO[3,4-*d*]PYRIMIDINES

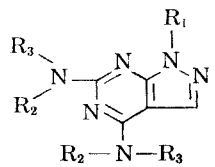
R_1	R_2	R_3	M.P. (°C.)	Yield (%)	U.v. Absorption λ_{max}, mμ Ethanol	ε	Recrystn.[a] Solvents	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	H	CH_3	239–240	51.4			C	42.6	4.05	35.2	42.8	4.38	35.1
CH_3	H	CH_2CH_3	211	44.2			C	45.6	4.75		45.3	4.64	
CH_3	H	$C(CH_3)_3$	162–163	42.4	284	10,500	J	50.3	5.85		50.9	4.92	
CH_3	H	$-(CH_2)_7CH_3$	87.5–88	66.0	284	10,000	L	56.9	7.52	23.6	56.6	8.03	23.4
CH_3	H	$C(CH_3)_2CH_2C(CH_3)_3$	183–184	89.5	285	19,200	K	56.9	7.52	23.6	56.9	7.74	23.1
CH_3	H	CH_2CH_2OH	238	95.0	282	15,500	G	42.2	4.44		42.2	4.34	
CH_3	H	$CH_2CH_2N(C_2H_5)_2$	89	58.5			G and H	51.0	6.78		51.3	6.67	

TABLE II (*Continued*)

R_1	R_2	R_3	M.P. (°C.)	Yield (%)	U.v. Absorption λ_{max}, mμ Ethanol	ϵ	Recrystn.[a] Solvents	Analyses, % Calcd. C	H	N	Found C	H	N
CH_3	H	$CH_2CH_2CH_2OCH(CH_3)_2$	117.5–119	43.0			G	50.8	6.40		50.3	6.05	
CH_3	H	$CH_2C_6H_5$	168	84.6	284	16,200	L	57.2	4.42		57.7	4.88	
CH_3	H	$CH_2C_6H_4Cl(p)$	201–202.5	74.3	283	17,600	B	50.7	3.60	22.7	51.2	3.74	23.0
CH_3	H	o-ClC_6H_4	224–225	85.6	285	15,900	M and A			23.7			23.4
CH_3	H	o-$CH_3C_6H_4$	235–237	37.2	284	20,000	B	57.1	4.43		57.2	4.38	
CH_3	H	$C_6H_3(CH_3)_2$(2,4)	241	56.5	284	20,400	B	58.5	4.91	24.3	58.8	4.67	24.0
CH_3	H	$C_6H_3(CH_3)_2$(2,5)	232	77.8	284	20,400	M	58.5	4.91	24.3	58.4	5.08	24.4
CH_3	H	$C_6H_3(CH_3)_2$(2,6)	242	70.7	283	14,600	B	58.5	4.91	24.3	58.6	4.98	24.0
CH_3	CH_2CH_3	C_6H_5	124–125	63.5	287	22,400	G	58.5	4.91		59.4	4.87	
CH_3	H	NH_2	>300	84.0	280	11,000	M	36.3	3.55		35.8	3.58	
C_6H_5	H	$CH_2CH_2CH_3$	186–187.5	64.5	242	34,000	C	58.5	4.91		58.5	5.20	
					292	17,100							
C_6H_5	H	$CH(CH_3)_2$	157–157.5	81.1	242	34,000	A and G	58.5	4.91		58.4	5.13	
					292	16,500							
C_6H_5	H	$C(CH_3)_3$	200–202	74.1	242	30,500	G	59.6	5.35	23.2	59.3	5.13	23.4
					291	16,200							
C_6H_5	H	$CH_2CH_2CH_2OCH(CH_3)_2$	129–130	69.0	243	32,600	G	59.4	5.83		60.0	6.10	
					291	16,600							
C_6H_5	H	CH_2CH_2OH	211.5–212.5	95.2	242	34,000	G	53.7	4.18	24.2	53.3	4.23	24.4
					291	18,900							
C_6H_5	H	2-Furfuryl	174–175.5	23.9	242	32,600	C	59.2	3.72		59.8	3.97	
					290	15,700							
C_6H_5	H	C_6H_5	281–284	66.0	245	29,800	M	63.6	3.77		64.0	3.89	
					307	27,200							
C_6H_5	H	$C_6H_3(CH_3)_2$(2,6)	218–219	83.5	243	33,600	B	65.4	4.62	20.0	65.4	4.83	20.0
					292	16,700							
C_6H_5	H	$C_6H_3(C_2H_5)_2$(2,6)	210–211.5	70.2	243	40,200	B	66.9	5.34		67.4	5.46	
					293	21,200							
C_6H_5	C_2H_5	C_6H_5	162–163.5	53.1	243	27,200	M and B	65.4	4.62		65.7	4.80	
					296	16,700							
C_6H_5	H	NH_2	>300	71.2	242	32,500	M	59.8	3.48		51.4	3.68	
					293	13,000							
C_6H_5	H	NHC_6H_5	268–269	56.4	243	46,000	M and B	60.6	3.90		60.3	4.02	
					291	17,600							

[a] Recrystallization solvents: A, water; B, ethanol; C, ethanol and water; G, methanol; H, toluene; J, methanol and water; K, benzene and ethanol; L, benzene and heptane; M, 2-ethoxyethanol.

TABLE III



SUBSTITUTED 4,6-DIAMINOPYRAZOLO[3,4-*d*]PYRIMIDINES

					U.v. Absorption				Re-crystn.[a]	Analyses, %					
					λ_{max}, mμ		λ_{max}, mμ			Calcd.			Found		
R_1	R_2	R_3	M.P. (°C.)	Yield (%)	pH 11	ε	Ethanol	ε	Sol-vents	C	H	N	C	H	N
CH_3	H	CH_2CH_3	140–141	57.2	232	35,200			C	54.5	7.32		54.6	7.12	
					261	12,000									
					283	13,600									
CH_3	CH_3	CH_3	128.5–129	92.3	240	30,400			G and A	54.5	7.32		54.5	7.45	
					286	10,500									
CH_3	H	$NHCH_3$	176	90.6					A	43.1	6.35	50.4	42.8	6.55	49.7
CH_3	H	C_6H_5	185–186	88.7	243	12,900			G	68.5	5.10		68.6	4.90	
					285	17,400									
CH_3	H	*o*-ClC_6H_4	161–161.5	80.0			270	32,000	M and A	56.2	3.66		56.0	3.82	
CH_3	H	*m*-ClC_6H_4	177–178.5	41.1			254	18,500	G	56.2	3.66		56.8	3.70	
							291	45,500							
CH_3	H	*p*-ClC_6H_4	202–204	48.1			255	18,500	B	56.2	3.66	21.8	56.2	3.70	22.0
							291	48,000							
CH_3	H	*p*-BrC_6H_4	201–202	21.5			255	17,600	B			17.7			17.6
							292	48,500							
CH_3	H	$C_6H_3(CH_3)_2$(2,4)	192.5–193.5	15.6			286	29,400	G and A	71.0	6.50		71.4	6.97	
CH_3	CH_3	C_6H_5	129–130	53.0			227	20,000	G	70.3	5.85		69.8	6.10	
							269	24,000							
C_6H_5	H	NH_2	217–219	50.4	368	21,000			B	51.6	4.72		51.6	4.80	
C_6H_5	H	$NHCH_3$	148–148.5	71.4			245	38,800	G and A	54.9	5.67	39.5	54.7	5.86	39.7
							293	18,200							
C_6H_5	H	$CH_2CH_2N(C_2H_5)_2.2HCl$	261–262.5		236	32,400	230	40,000	G	55.6	7.71		55.2	7.72	
					287	16,400	282	16,500							

[a] Recrystallization Solvents: A, water; B, ethanol; C, ethanol and water; G, methanol; M, 2-ethoxyethanol.

lized from methanol and water to give white, silky needles, m.p. 211.5–212.5°. The yield was 5.2 g. (95%).

Anal. Calcd. for $C_{13}H_{12}N_5OCl$: C, 53.7; H, 4.2; N, 24.2. Found: C, 53.3; H, 4.2; N, 24.4.

Preparation of 1-alkyl(aryl)-4,6-bis(substituted amino)-pyrazolo[3,4-d]pyrimidines. See Table III. The preparation of the bis-substituted amino derivatives can be illustrated by the following examples:

4,6-Bis(hydrazino)-1-phenylpyrazolo[3,4-d]pyrimidine. Six grams of 4,6-dichloro-1-phenylpyrazolo[3,4-*d*]pyrimidine was added to 60 g. of 70% hydrazine hydrate in 100 ml. ethanol. The mixture was boiled gently on the steam bath. A white precipitate appeared after 2 min. of heating and slowly redissolved with further heating. The solution was reduced to two thirds of its original volume, and the product crystallized on cooling. Recrystallization from ethanol gave 3 g. (51%) of glistening plates, m.p. 217–219°.

Anal. Calcd. for $C_{11}H_{12}N_8$: C, 51.6; H, 4.7. Found: C, 51.6; H, 4.8.

4,6-Bis(p-chloroanilino)-1-methylpyrazolo[3,4-d]pyrimidine. A solution of 8 g. of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]-pyrimidine and 15 g. of *p*-chloroaniline in 200 ml. of absolute ethanol was refluxed for 3 hr. A white precipitate appeared in the hot solution. The product was filtered and added to 100 ml. of ethanol containing 10 g. of potassium hydroxide. The mixture was boiled for 15 min. and filtered. To the filtrate was added 100 ml. of water, and the mixture was allowed to stand overnight. The product was filtered, washed with water, and recrystallized from 95% ethanol to give 7.3 g. (48%) of small, white needles, m.p. 202–204°.

Anal. Calcd. for $C_{18}H_{14}N_6Cl_2$: C, 56.2; H, 3.6; N, 21.8. Found: C, 56.2; H, 3.7; N, 22.0.

4,6-Bis(dimethylamino)-1-methylpyrazolo[3,4-d]pyrimidine. To 20 ml. of ethanol and 60 g. of 25% aqueous dimethylamine was added 10 g. of 1-methyl-4,6-dichloropyrazolo-[3,4-*d*]pyrimidine. The mixture was boiled gently on a steam bath to dryness. Another 40 g. of 25% aqueous methylamine was added, and the solution was again evaporated to dryness. The residue was recrystallized from aqueous methanol to give 10 g. (92.3%) of small, white needles, m.p. 128.5–129°.

Anal. Calcd. for $C_{10}H_{16}N_6$: C, 54.6; H, 7.3. Found: C, 54.5; H, 7.5.

Preparation of 4-amino-6-β-hydroxyethylamino-1-methylpyrazolo[3,4-d]pyrimidine. Seven g. of ethanolamine was added to 120 ml. of 2-ethoxyethanol containing 5 g. of 4-amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (VI). The mixture was refluxed for 6 hr. Excess solvent was distilled off under reduced pressure and the sirupy residue poured into a beaker. To this crude product was added a little benzene followed by a few drops of methanol, and the residue solidified after a few minutes. The product was filtered and recrystallized from a mixture of benzene and methanol to give 3.4 g. (60%) of white crystals, m.p. 189–191.5°.

Anal. Calcd. for $C_8H_{12}N_6O$: C, 46.1; H, 5.8. Found: C, 46.1; H, 6.3.

Preparation of 4,6-bis(methylthio)-1-methylpyrazolo[3,4-d]-pyrimidine (XVI, $R_1 = SCH_3$). Four g. of 4,6-dimercapto-1-methylpyrazolo[3,4-*d*]pyrimidine was added to a mixture of 2 g. of potassium hydroxide, 10 g. of methyl iodide and 100 ml. of water. To this mixture was added, with stirring, 100 ml. of methanol. The solution was stirred for 30 min., and a white solid separated on standing. The product was filtered, washed with water, and dissolved in hot methanol. The solution was filtered, and to the filtrate was added 5 ml. of 1% potassium hydroxide solution. The product crystallized slowly as white plates and was filtered and washed with water to yield 4 g. (87.8%), m.p. 100.5–101.5°.

Anal. Calcd. for $C_8H_{10}N_4S_2$: C, 42.5; H, 4.5; N, 24.8. Found: C, 42.2; H, 4.5; N, 24.3.

Preparation of 4,6-dimethoxy-1-methylpyrazolo[3,4-d]pyrimidine (XVI, $R_1 = OCH_3$). To 6 g. of 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine (VI, R = CH_3), dissolved in 50 ml. of methanol, precooled to 10°, was slowly added, with shaking, 50 ml. of a sodium methoxide solution (prepared by dissolving 2 g. of sodium in 50 ml. of methanol). The mixture was allowed to stand at room temperature for 30 min. with occasional shaking and finally heated for 10 min. on the steam bath. The sodium chloride was filtered, and 10 ml. of water was added to the filtrate. White needles separated after the solution was cooled. The product was filtered, washed with water, and recrystallized from methanol to give 2.5 g. (43.6%) of white needles, m.p. 106°.

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.5; H, 5.2; N, 28.8. Found: C, 49.8; H, 5.3; N, 28.6.

Preparation of 4-hydroxy-1-methyl-6-methylthiopyrazolo-[3,4-d]pyrimidine. To 7.2 g. (0.04 mole) of 4-hydroxy-6-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine (XII) in 100 ml. of 2*N* potassium hydroxide solution was slowly added, with stirring, 5.1 g. (0.04 mole) of dimethylsulfate. The temperature was kept between 25–40°. The mixture was stirred for 1 hr. and then allowed to stand at room temperature for 48 hr. It was then acidified with glacial acetic acid to *p*H 5. A white substance was gradually formed. The product was filtered and recrystallized from a mixture of ethanol and water to give 2 g. (26%) of white needles, m.p. 258–260°.

Anal. Calcd. for $C_7H_8N_4OS$: C, 42.9; H, 4.1; N, 28.6. Found: C, 43.1; H, 4.4; N, 29.0.

Preparation of 4-amino-1-methyl-6-methoxypyrazolo[3,4-d]-pyrimidine (III, R = CH_3). To 100 ml. of methanol was added 5.5 g. of 4-amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (II, R = CH_3). The mixture was added slowly to 100 ml. of methanol to which had previously been added 2 g. of sodium. The reaction mixture was allowed to stand at room temperature for 24 hr. followed by 30 min. of heating on a steam bath. Sodium chloride was filtered, and the product which separated from the cooled filtrate was recrystallized from water to give 3.1 g. (58%) of white needles, m.p. 285–286°.

Anal. Calcd. for $C_7H_9N_5O$: C, 46.8; H, 5.1. Found: C, 46.5; H, 4.8.

Preparation of 4-amino-6-mercapto-1-methylpyrazolo[3,4-d]pyrimidine (VI, R = CH_3). A mixture of 8 g. of 4-amino-6-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine (II, R = CH_3) and 100 ml. of 3*N* potassium hydrosulfide was heated at 110° in a bomb for 8 hr. The solid potassium salt which appeared on cooling was filtered and dissolved in water. The resulting solution was acidified with glacial acetic acid and the solid product filtered and reprecipitated twice from potassium hydroxide solution with glacial acetic acid to give 3.9 g. (49%) of light-yellow precipitate, m.p. >310°.

Anal. Calcd. for $C_6H_7N_5S$: C, 39.8; H, 3.9. Found: C, 39.7; H, 3.8.

Preparation of 4-amino-1-methylpyrazolo[3,4-d]pyrimidine (IX, R = CH_3) *from 4-amino-6-mercapto-1-methylpyrazolo-[3,4-d]pyrimidine* (VI, R = CH_3). To 2.9 g. of 4-amino-6-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine, dissolved in 200 ml. of concentrated ammonium hydroxide, were added 1 l. of 95% ethanol and 20 g. of Raney Nickel. The mixture was refluxed for 48 hr., filtered, and the filtrate concentrated to 100 ml. White needles separated from the chilled solution. The product was filtered and recrystallized from ethanol to give 1.2 g. of 4-amino-1-methylpyrazolo[3,4-*d*]pyrimidine, m.p. 267–268°. This compound was identical to that product prepared from 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine,[5] as judged on the basis of mixed melting point data.

Preparation of 4-hydroxy-6-mercapto-1-methylpyrazolo[3,4-d]pyrimidine (XII, R = CH_3). *Method 1.* Fifty-five g. of 5-amino-1-methylpyrazole-4-carboxamide was fused with 110 g. of thiourea at 210° for 2 hr. The fused product was dissolved in potassium hydroxide solution followed by reprecipitation with glacial acetic acid. The reprecipitation was repeated twice and 41 g. of white solid obtained, m.p. >300°.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.6; H, 3.3; N, 30.8. Found: C, 39.8; H, 3.9; N, 30.5.

Method 2. A mixture of 5.5 g. of 6-chloro-4-hydroxy-1-

methylpyrazolo[3,4-*d*]pyrimidine, 3 g. of thiourea, and 100 ml. of absolute ethanol was refluxed for 5 hr. The solid product was filtered and reprecipitated from dilute potassium hydroxide solution by glacial acetic acid to give 4.0 g. (73.6%) of white solid, m.p. >300°.

This preparation was found to be identical to the compound made by Method 1 on the basis of identical ultraviolet absorption spectra at *p*H 1 and *p*H 11.

Preparation of 6-chloro-4-mercapto-1-methylpyrazolo[3,4-d]pyrimidine (XIV, R = CH_3). To 200 ml. of 0.5*N* potassium hydrosulfide was added 5 g. of finely powdered 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine. The mixture was stirred at 0° for 15 min. and then allowed to stand at room temperature for 2 hr. The mixture was filtered and the filtrate acidified with glacial acetic acid. Four and one-half grams (46%) of white solid was obtained, m.p. 223° (dec.).

Anal. Calcd. for $C_6H_5N_4SCl$: N, 27.9. Found: N, 27.7.

Preparation of 6-ethoxy-4-mercapto-1-methylpyrazolo[3,4-d]pyrimidine (XV). To 100 ml. of absolute ethanol containing 2.0 g. of sodium was added 5.3 g. of powdered 6-chloro-4-mercapto-1-methylpyrazolo[3,4-*d*]pyrimidine (XIII). The mixture was allowed to stir at room temperature for 1 hr. followed by 30 min. of heating on the steam bath. Sodium chloride was filtered and filtrate acidified with dilute acetic acid to give 4.5 g. (81%) of small, yellow plates, m.p. 240° (dec.).

Anal. Calcd. for $C_8H_{10}N_4S$: C, 45.6; H, 4.8. Found: C, 45.2; H, 4.9.

Preparation of 6-chloro-4-ethylthio-1-methylpyrazolo[3,4-d]-pyrimidine (XIX). Ten g. of finely powdered 4,6-dichloro-1-methylpyrazolo[3,4-*d*]pyrimidine was added to a solution of 12 g. of potassium hydroxide, 20 g. of ethylmercaptan, and 50 ml. of water. The mixture was stirred at room temperature for 3 hr. A white precipitate was obtained which was filtered and recrystallized from absolute ethanol to give 8.5 g. (76%) of white needles, m.p. 112–113°.

Anal. Calcd. for $C_8H_9N_4SCl$: C, 42.1; H, 4.0. Found: C, 42.4; H, 4.1.

Preparation of 6-ethoxy-4-ethylthio-1-methylpyrazolo[3,4-d]-pyrimidine (XX). Five g. of 6-chloro-4-ethylthio-1-methylpyrazolo[3,4-*d*]pyrimidine was added to 100 ml. of absolute ethanol containing 2.0 g. of dissolved sodium. The mixture was allowed to stand at room temperature for 5 hr. It was then warmed on a steam bath for 3 min. and filtered. White needles, m.p. 92–93°, were obtained from the cooled filtrate. The yield was 3.0 g. (58%).

Anal. Calcd. for $C_{10}H_{14}N_4OS$: C, 50.5; H, 5.9. Found: C, 50.4; H, 6.1.

TEMPE, ARIZ.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Condensations Involving the Metalation of the 3-Position of 3-Phenylphthalide by Means of Alkali Amides. Carbonation of Phthalide[1]

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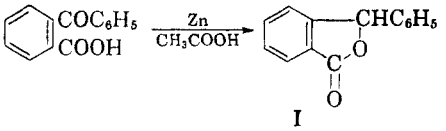
3-Phenylphthalide was metalated at its 3-position by means of an alkali amide in liquid ammonia, and the resulting alkali derivative was employed in several types of carbon-carbon condensations in this medium or in ether. These condensations included carbonation, benzylation, benzoylation, and conjugate addition. The structure of the acid obtained on carbonation was established by the Hofmann rearrangement of the corresponding acid amide. The ketone produced on benzoylation was cleaved by means of potassium hydroxide solution.

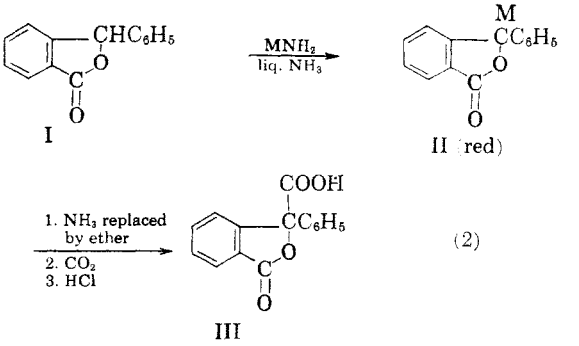
Although 3-phenylphthalide (I) is readily prepared by the reduction of *o*-benzoylbenzoic acid by means of zinc and acetic acid (Equation 1),[2,3] this active hydrogen compound appears not to have been employed previously in condensations involving the ionization of its 3-hydrogen (γ-hydrogen).



(1)

I

In the present investigation the 3-position of 3-phenylphthalide was metalated by means of alkali amides in liquid ammonia, and the resulting red alkali derivative employed in several types of carbon-carbon condensations. One of these reactions involved carbonation to form lactone acid III which was obtained in yields of 80–87% by means of potassium amide, sodium amide, or lithium amide (Equation 2, M = K, Na, or Li).



I II (red) III

(2)

(1) Supported by the National Science Foundation.

(2) F. Ullmann, *Ann.*, **291**, 23 (1896).

(3) Also, we have obtained a 48% yield of 3-phenylphthalide (I) along with a 25% yield of *o*-benzylbenzoic acid on reducing *o*-benzoylbenzoic acid with zinc-amalgam and hydrochloric acid (Clemmensen method). These two compounds were readily separated by means of sodium bicarbonate solution in which I was insoluble. Earlier workers [H. L. Bradlow and C. A. VanderWerf, *J. Am. Chem. Soc.*, **69**, 1254 (1947)] have reported that, under certain conditions, this method produces *o*-benzylbenzoic acid in yields of 70–75%.