[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

The Reaction of Malononitrile with Substituted Hydrazines: New Routes to 4-Aminopyrazolo[3,4-d]pyrimidines[1,2]

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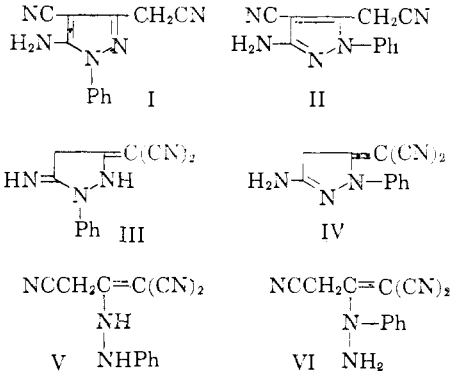
The reaction of malononitrile or malononitrile dimer (1,1,3-tricyano-2-aminopropene-1) with phenylhydrazine and methylhydrazine is shown to give 1-phenyl- and 1-methyl-3-cyanomethyl-4-cyano-5-aminopyrazole (I and XVIII), respectively. The structure of I is established by degradation to 1-phenyl-3-methyl-5-aminopyrazole (XIV), and the structure of XVIII is established by degradation to 1,3-dimethyl-4-nitroso-5-pyrazolone (XXIX). These readily available pyrazoles are versatile intermediates for the synthesis of condensed pyrazole heterocycles, including a number of derivatives of 1-phenyl- and 1-methyl-4-aminopyrazolo[3,4-d]pyrimidine.

In the preceding paper,[4] the reaction of malononitrile with hydrazine was shown to yield 3-cyanomethyl-4-cyano-5-aminopyrazole and not 3,5-diaminopyrazole as previously claimed.[5] The present paper discusses the structures of the products formed by reaction of malononitrile with two representative substituted hydrazines, phenylhydrazine and methylhydrazine, and illustrates the usefulness of the resulting products as intermediates for the synthesis of condensed pyrazole heterocycles.

The reaction of malononitrile or malononitrile dimer[4] with phenylhydrazine led to a colorless, crystalline solid, m.p. 166°, with the molecular formula $C_{12}H_9N_5$.[6] Of the six possible formulations (I–VI) for this product, only I and II are consistent with all of the following observations: (1) the compound is recovered unchanged after prolonged heating in ethanolic sodium ethoxide solution (excluding structures V and VI); (2) the compound shows infrared absorption bands at 2.93, 3.05 and



3.15 μ (N–H bands) and two nitrile bands, one at 4.46 (unconjugated) and one at 4.54 μ (conjugated) (excluding structures III and IV); (3) the ultraviolet absorption spectrum given by the compound shows only decreasing absorption with increasing wave length, with no maximum above 220 mμ (excluding structures V and VI, since malononitrile dimer shows a strong absorption maximum at 273 mμ); (4) both the infrared and ultravolet absorption spectra given by the compound are similar to the spectra given by the product of the reaction of malononitrile with hydrazine itself, which has been shown[4] to be 3-cyanomethyl-4-cyano-5-aminopyrazole. The choice is thus narrowed to structures I and II. In the subsequent discussion of the proof of structure of the compound $C_{12}H_9N_5$, structure I, which will be shown to be correct, will be employed throughout for the purposes of both brevity and clarity.

Initial attempts to degrade I to a simple pyrazole were unsuccessful. Hydrolysis with 5% sodium hydroxide yielded 1-phenyl-3-carboxymethyl-4-carboxamido-5-aminopyrazole (VII), but attempted decarboxylation of this compound led only to decomposition. Conversion of I to the imino ether IX, followed by mild aqueous hydrolysis to the ester X, and finally saponification with sodium carbonate, gave 1-phenyl-3-carboxymethyl-4-cyano-5-aminopyrazole (XI), but attempted decarboxylation of XI resulted in ring closure to give 2-phenyl-3-amino-4,6-dihydroxypyrazolo(4,3-c)pyridine (VIII). Compound VIII could also be formed by treatment of I or VII with strong acids. Hydrolysis of X with dilute sodium hydroxide gave VII. This observation confirms the assigned positions of the carboxamido and carboxyl groups of VII, since the infrared spectrum of X definitely places the nitrile group in the 4-position of the pyrazole ring (conjugated nitrile at 4.51 μ). A projected Curtius degradation sequence starting with the ester X likewise proved to be fruitless, for it was not possible to convert it either to the amide or to the hydrazide. For example, X was recovered unchanged after heating with alcoholic ammonia at 150° for 8 hours. It seems probable that removal of a proton from X yields a resonance stabilized anion (XII) which resists further nucleophilic attack by ammonia or hydrazine.

Complete hydrolysis of both nitrile groups of I therefore appeared to be a necessary prelude to further degradation of the molecule. Treatment of I with boiling 30% sodium hydroxide for 8–10 hours resulted in vigorous evolution of ammonia and the formation of a monocarboxylic acid, $C_{11}H_{11}N_3O_2$. Proof that this compound was 1-phenyl-3-carboxymethyl-5-aminopyrazole (XIII) and not the isomeric 1-phenyl-3-methyl-4-carboxy-5-aminopyrazole(XV) was obtained as follows:

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(2) Presented before the Division of Organic Chemistry at the 2nd Delaware Valley Meeting of the A.C.S., February 5, 1958, in Philadelphia, Pa., and before the Division of Organic Chemistry at the 133rd Annual ACS Meeting, April 13–18, 1958, in San Francisco, Calif.

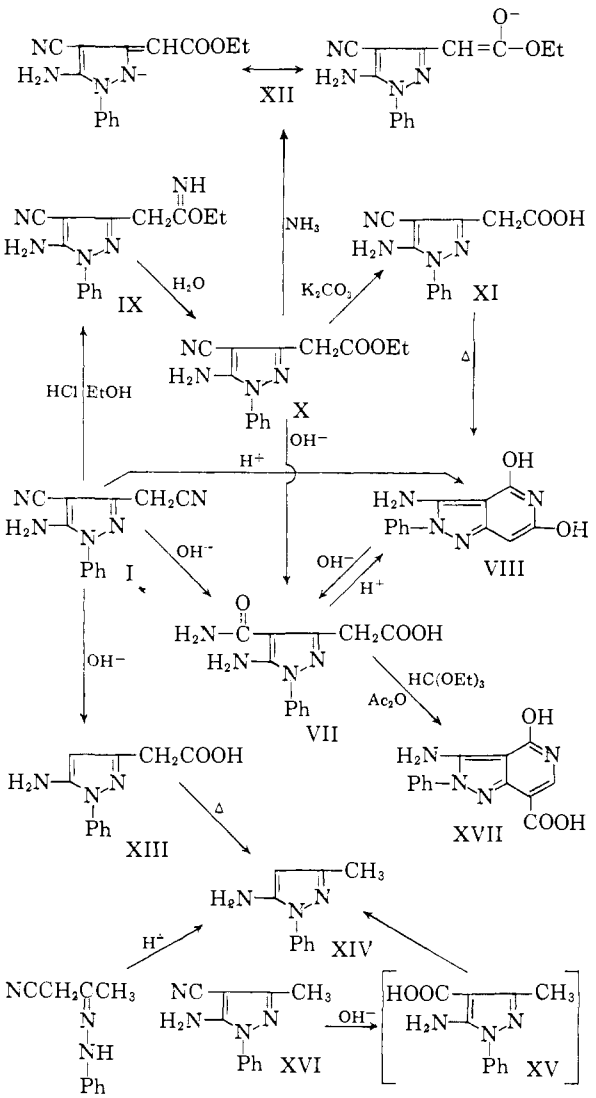
(3) Visiting Scholar from the University of Marburg, sponsored by Der Stifterverband für die Deutsche Wissenschaft.

(4) E. C. Taylor and K. S. Hartke, THIS JOURNAL, **81**, 2452 (1959).

(5) R. von Rothenburg, *Ber.*, **27**, 685 (1894).

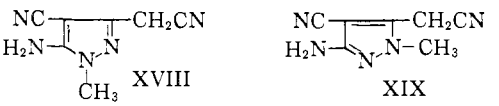
(6) von Rothenburg (ref. 5) reported that the reaction of malononitrile with phenylhydrazine yielded a dark brown oil for which no structure was suggested.

Decarboxylation of the monocarboxylic acid (XIII or XV) by heating at 200° *in vacuo* yielded 1-phenyl-3-methyl-5-aminopyrazole (XIV), which was prepared independently from the known[7] 1-phenyl-3-methyl-4-cyano-5-aminopyrazole (XVI) by alkaline hydrolysis. All attempts to isolate the intermediate 4-carboxylic acid (XV) in this latter reaction failed, for the compound decarboxylated spontaneously at room temperature even in dilute acetic acid solution. Thus, the monocarboxylic acid formed by hydrolysis of I must have been XIII. Final proof that the product of the decarboxylation of XIII was indeed 1-phenyl-3-methyl-5-aminopyrazole (XIV) was obtained by comparison of this product with an authentic sample[8] of XIV prepared by acid cyclization of the phenylhydrazone of cyanoacetone.



On the basis of the above degradation sequence, the structure of the compound $C_{12}H_9N_5$, formed by the reaction of malononitrile or malononitrile dimer with phenylhydrazine, is firmly established to be 1-phenyl-3-cyanomethyl-4-cyano-5-aminopyrazole (I).[9]

The reaction of malononitrile or malononitrile dimer with methylhydrazine yielded a white, crystalline solid, m.p. 178°, with the molecular formula $C_7H_7N_5$. As a result of arguments similar to those employed previously in the discussion of the structure of I, it was apparent that this product was either 1-methyl- or 2-methyl-3-cyanomethyl-4-cyano-5-aminopyrazole (XVIII or XIX, respectively). It was unfortunately not possible to assign structure XVIII to this product by analogy with the established structure I for the phenylhydrazine product because of the different basicities of the nitrogen atoms in methyl- and phenylhydrazine. Thus, aromatic hydrazines are known to acylate exclusively on the β-nitrogen,[10,11] while aliphatic hydrazines react predominantly at the more basic α-nitrogen.[11-13] This difference is also manifested in pyrazole syntheses. For example, reaction of ethyl β-amino-β-ethoxyacrylate with phenylhydrazine yields 1-phenyl-3-amino-5-pyrazolone, while reaction with methylhydrazine leads predominantly to the other isomer, 1-methyl-3-hydroxy-5-iminopyrazole.[14,15] An independent structure proof for the methylhydrazine product $C_7H_7N_5$ was therefore mandatory. However, in order to simplify the following discussion, the methyl group will be assigned its correct position (structure XVIII).



XVIII XIX

A number of the reactions of XVIII proved to be analogous to the reactions previously discussed of I. For example, the action of dilute alkali on XVIII led to 1-methyl-3-carboxymethyl-4-carboxamido-5-aminopyrazole (XX), while treatment with strong acids yielded 2-methyl-3-amino-4,6-dihydroxypyrazolo(4,3-c)pyridine (XXI); XX was converted with a mixture of ethyl orthoformate and acetic anhydride by cyclization across the active methylene group and the carboxamido group to 2-methyl-3-amino-4-hydroxy-7-carboxypyrazolo(4,3-c)pyridine (XXII). A similar reaction carried out with VII led to the corresponding phenyl derivative XVII. Hydrolysis of XVIII with 30% sodium hydroxide yielded a monocarboxylic acid which was shown to be 1-methyl-3-carboxymethyl-5-aminopyrazole (XXIII) rather than the isomeric 1,3-dimethyl-4-carboxy-5-aminopyrazole (XXVI) by arguments similar to those employed in the establishment of the structure of XIII. Thus, 1,3-dimethyl-

(7) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).
(8) E. Mohr, *J. prakt. Chem.*, **79**, 1 (1909).
(9) Since the initial presentation of this material (see ref. 2), the reaction of malononitrile dimer with phenylhydrazine has been described (R. A. Carboni, D. D. Coffman and E. G. Howard, THIS JOURNAL, **80**, 2838 (1958)) as leading to a compound believed to be 2-phenyl-3-cyanomethyl-4-cyano-5-aminopyrazole (II), although it was stated that the isomeric structure I could not be eliminated as a possibility. It is now shown that the product of this reaction is indeed I.
(10) E. Fischer, *Ann.*, **190**, 67 (1878).
(11) M. T. Folpmers, *Rec. trav. chim.*, **34**, 34 (1915).
(12) A. Michaelis and E. Hadanck, *Ber.*, **41**, 3285 (1909).
(13) R. L. Hinman and D. Fulton, THIS JOURNAL, **80**, 1895 (1958).
(14) A. Weissberger, H. D. Porter and W. A. Gregory, *ibid.*, **66**, 1851 (1944).
(15) B. Graham, H. D. Porter and A. Weissberger, *ibid.*, **71**, 983 (1949).

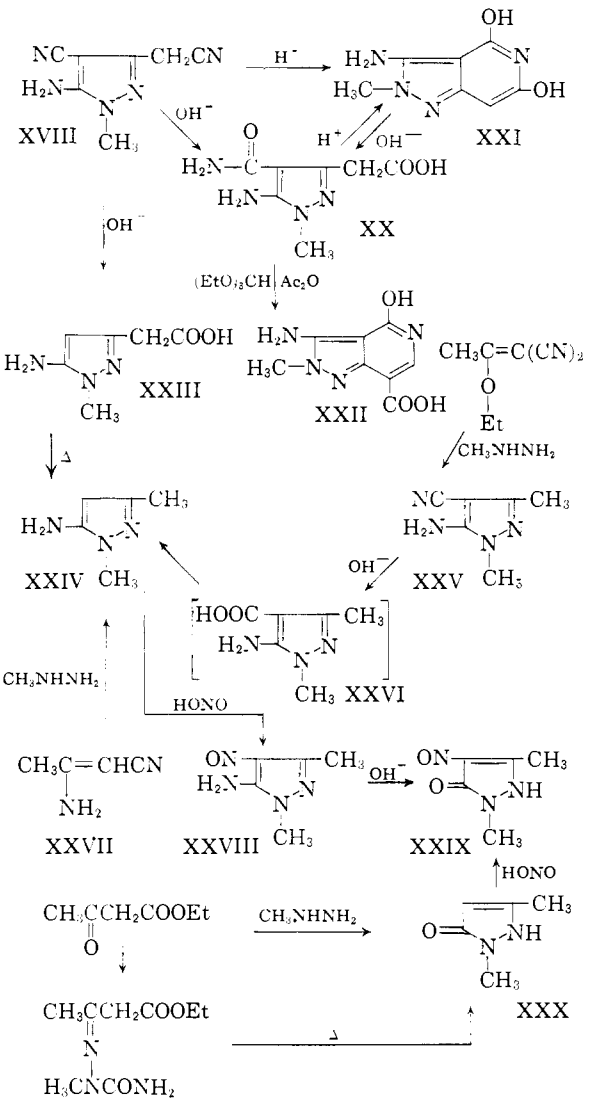
4-cyano-5-aminopyrazole (XXV)[7] was prepared from methylethoxymethylenemalononitrile and methylhydrazine and hydrolyzed with 30% sodium hydroxide. The only product which could be isolated was 1,3-dimethyl-5-aminopyrazole (XXIV), for the intermediate 4-carboxylic acid XXVI proved to be extremely unstable and decarboxylated spontaneously at room temperature. Conversion of XXIII to XXIV was achieved by heating at 200° *in vacuo*. Finally, a third independent synthesis of XXIV was carried out by treating the dimer of acetonitrile (1-cyano-2-aminopropene-1) (XXVIII) with methylhydrazine.

None of the above syntheses, however, establishes with certainty the position of the N-methyl group in XXIV. The structure of 1,3-dimethyl-4-cyano-5-aminopyrazole (XXV) had been assigned by analogy with the phenyl isomer, whose structure had been rigorously established,[7] but it has already been pointed out that analogies based on the assumption that phenylhydrazine and methylhydrazine react similarly are not compelling. The synthesis of XXIV from the dimer of acetonitrile and methylhydrazine confirms the pyrazole nature of the product, but sheds no light on the position of the N-methyl group. It remained, therefore, to establish with certainty the structure of 1,3-dimethyl-5-aminopyrazole (XXIV).

Both 1,3-dimethyl-5-pyrazolone (XXX)[16-18] and 1,5-dimethyl-3-pyrazolone (XXXI)[19] are known, and it was thought the establishment of a relationship between XXIV and one or the other of these compounds would serve to establish its structure with certainty. Therefore, XXIV was nitrosated to 1,3-dimethyl-4-nitroso-5-aminopyrazole (XXVIII), which was smoothly converted by heating with alkali to 1,3-dimethyl-4-nitroso-5-pyrazolone (XXIX). 1,3-Dimethyl-5-pyrazolone (XXX) was then prepared by the known method[18] from ethyl acetoacetate and methylhydrazine, and nitrosation yielded a product identical in all respects with XXIX.

A careful reading of the literature revealed, however, that even the long accepted structures of XXX and XXXI had never been firmly established. Knorr[16] assigned the structure 1,3-dimethyl-5-pyrazolone (XXX) to the product of the reaction of ethyl acetoacetate and methylhydrazine apparently on the assumption that the first step in the reaction must involve the formation of the methylhydrazone of ethyl acetoacetate. The structure of the isomeric 1,5-dimethyl-3-pyrazolone (XXXI) was then apparently assigned by default.[19] Fortunately, an unequivocal confirmation of the correctness of Knorr's structural assignment was possible. It has been reported[20] that 3-methyl-5-pyrazolone may be prepared by gentle pyrolysis of the semicarbazone of ethyl acetoacetate. We therefore prepared the N-methylsemicarbazone of ethyl acetoacetate, which upon heating was converted into 1,3-dimethyl-5-pyrazolone (XXX), identical in all respects with Knorr's product.

(16) L. Knorr, *Ann.*, **279**, 232 (1894).
(17) L. Wolff and W. Schreiner, *Ber.*, **41**, 550 (1908).
(18) K. v. Auwers and F. Niemeyer, *J. prakt. Chem.*, **110**, 153 (1925).
(19) C. A. Rojahn, *Ber.*, **55**, 2959 (1922).
(20) J. Thiele and O. Stange, *Ann.*, **283**, 1 (1894).



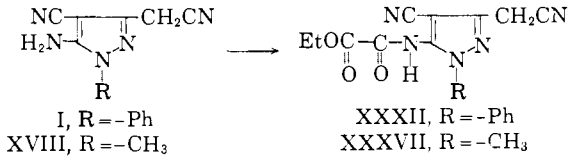
The product of the reaction of malononitrile or malononitrile dimer with methylhydrazine is thus conclusively established as 1-methyl-3-cyanomethyl-4-cyano-5-aminopyrazole (XVIII).

Considerable recent attention has been given to the 4-aminopyrazolo(3,4-d)pyrimidine system because of the significant antimitotic activity exhibited by a number of its derivatives.[21] The reaction of malononitrile or malononitrile dimer with substituted hydrazines has been shown to lead directly and in good yield to pyrazole intermediates (I and XVIII) potentially capable of ready conversion to this class of condensed pyrazole heterocycle. We therefore investigated methods for their possible utilization for such syntheses.

1-Phenyl-3-cyanomethyl-4-cyano-5-aminopyrazole (I), upon treatment with diethyl oxalate in the presence of potassium ethoxide, yielded an ethoxalyl derivative to which structure XXXII was assigned on the basis of its subsequent reactions. Treatment of XXXII in tetrahydrofuran solution with diazomethane yielded a monomethyl

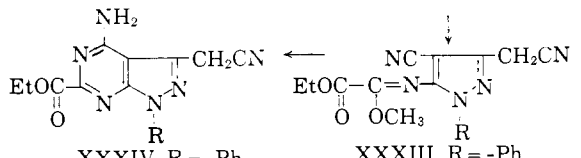
(21) H. E. Skipper, R. K. Robins, J. R. Thomson, C. C. Cheng, R. W. Brockman and F. M. Schabel, Jr., *Cancer Research*, **17**, 579 (1957), and references cited therein.

derivative which can only be 1-phenyl-3-cyanomethyl-4-cyano-5-carbethoxymethoxymethyleneaminopyrazole (XXXIII), since its infrared spectrum shows only one carbonyl peak (5.73 μ) and no N–H band. By contrast, XXXII shows two carbonyl bands (5.64 and 5.76 μ) and one N–H band (3.12 μ), thus conclusively placing the position of methylation on oxygen rather than on nitrogen. Finally, treatment of XXXIII with alcoholic ammonia resulted in a facile ring closure to give 1-phenyl-3-cyanomethyl-4-amino-6-carbethoxypyrazolo(3,4-d)pyrimidine (XXXIV) in almost quantitative yield. The infrared spectrum of XXXIV indicated the loss of the conjugated nitrile group and the retention of the unconjugated ni-



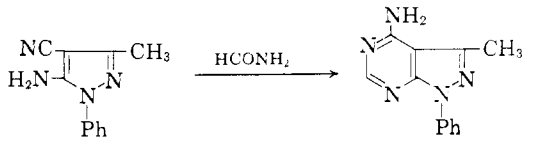
I, R = –Ph
XVIII, R = –CH_3

XXXII, R = –Ph
XXXVII, R = –CH_3



XXXIV, R = –Ph
XXXIX, R = –CH_3

XXXIII, R = –Ph
XXXVIII, R = –CH_3



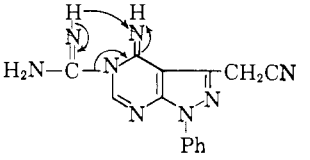
XXXVI

XXXV

trile group (4.42 μ), and the appearance of strong N–H bands (2.86, 3.06 and 3.22 μ) indicative of a substituent amino grouping. The ultraviolet absorption spectrum of XXXIV was very similar to the spectrum given by 1-phenyl-3-methyl-4-aminopyrazolo(3,4-d)pyrimidine (XXXV), which was prepared as a model compound by treatment of 1-phenyl-3-methyl-4-cyano-5-aminopyrazole (XXXVI) with formamide, except that the expected bathochromic effect of the 6-carbethoxy grouping was manifested by a shift of the entire spectrum to longer wave lengths.

An identical series of reactions was carried out starting with 1-methyl-3-cyanomethyl-4-cyano-5-aminopyrazole (XVIII), except that neither the ethoxalyl derivative XXXVII nor the carbethoxymethoxymethyleneamino derivative XXXVIII could be obtained crystalline. The entire reaction sequence leading to 1-methyl-3-cyanomethyl-4-amino-6-carbethoxypyrazolo(3,4-d)pyrimidine (XXXIX) was therefore carried out without isolation of the intermediates XXXVII and XXXVIII.

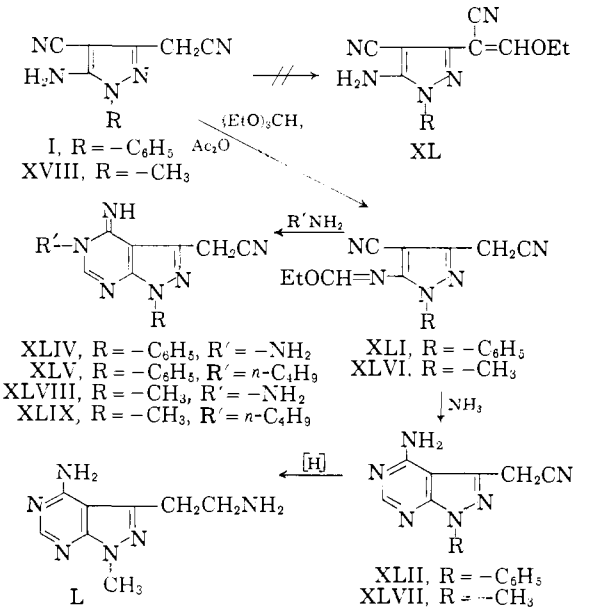
Treatment of I with a mixture of ethyl orthoformate and acetic anhydride yielded an ethoxymethylene derivative which could have been either XL or XLI, depending on whether the active methylene group or the amino group of I had participated in the reaction. The product was shown to be XLI by examination of its infrared spectrum and by its subsequent reactions. The strong N–H bands present in the spectrum of I were missing in the ethoxymethylene derivative, and the positions of the nitrile bands were unchanged, thus conclusively eliminating XL from consideration. The action of ethanolic ammonia on XLI at room temperature then led to the separation in almost quantitative yield of 1-phenyl-3-cyanomethyl-4-aminopyrazolo-(3,4-d)pyrimidine (XLII). As predicted, the ultraviolet absorption spectrum of XLII was almost superimposable with the spectrum of XXXV. Compound XLII was also formed by treatment of XLI with guanidine, apparently by elimination of cyanamide from the intermediate XLIII. Treatment of XLI with hydrazine and *n*-butylamine yielded 1-phenyl-3-cyanomethyl-4-imino-5-amino-4,5-dihydropyrazolo(3,4-d)pyrimidine (XLIV) and 1-phenyl-3-cyanomethyl-4-imino-5-(*n*-butyl)-4,5-dihydropyrazolo(3,4-d)pyrimidine (XLV), respectively.



XLIII

By a similar sequence of reactions, 1-methyl-3-cyanomethyl-4-cyano-5-aminopyrazole (XVIII) was converted into the pyrazolo(3,4-d)pyrimidines XLVII, XLVIII and XLIX.

The conversion of aromatic *o*-aminonitriles into systems containing a fused 4-amino- or 4-iminopyrimidine ring *via* an intermediate ethoxymethyleneamino derivative (such as XLI and XLVI) is somewhat similar to the method recently exploited so successfully by Shaw[22] for the synthesis of pyrimidine nucleosides, and provides an attractive potential route from the appropriate *o*-aminonitriles to glycosides of systems containing a fused pyrimi-



I, R = $-C_6H_5$
XVIII, R = $-CH_3$

XL

XLIV, R = $-C_6H_5$, R′ = $-NH_2$
XLV, R = $-C_6H_5$, R′ = n-C_4H_9
XLVIII, R = $-CH_3$, R′ = $-NH_2$
XLIX, R = $-CH_3$, R′ = n-C_4H_9

XLI, R = $-C_6H_5$
XLVI, R = $-CH_3$

L

XLII, R = $-C_6H_5$
XLVII, R = $-CH_3$

(22) G. Shaw in "Current Trends in Heterocyclic Chemistry," ed. by A. Albert, G. M. Badger and C. W. Shoppee, Butterworths Scientific Publications, London, 1958, p. 122.

dine ring, such as purines, pteridines and pyrazolo-(3,4-d)pyrimidines. We hope to report on these extensions of the above reaction sequences in a later communication.

A group of pyrazolo(3,4-d)pyrimidines of considerable potential physiological interest are the 3-(2-aminoethyl) derivatives, available by reduction of the 3-cyanomethyl grouping. This class of compound is illustrated by 1-methyl-3-(2-aminoethyl)-4-aminopyrazolo(3,4-d)pyrimidine (L), which was prepared in high yield by catalytic reduction of XLVII. It is intriguing to note that L might be considered to be a potential analog not only of the purines, but also of tryptamine and serotonin.

Experimental[23]

1-Phenyl-3-cyanomethyl-4-cyano-5-aminopyrazole (I). Method A.—A mixture of 1.32 g. (0.02 mole) of malononitrile, 1.09 g. (0.01 mole) of phenylhydrazine, and 10 ml. of ethanol was heated under reflux for 8 hours. Cooling caused the separation of a mass of red-brown crystals which were collected by filtration and washed with cold ethanol. An additional crop of crystals was obtained by concentration of the filtrate followed by addition of a few drops of water (total yield 0.85 g., 38%). Recrystallization from ethanol with the use of charcoal yielded white needles, m.p. 166°.

Anal. Calcd. for $C_{12}H_9N_5$: C, 64.6; H, 4.1; N, 31.4. Found: C, 64.6; H, 4.1; N, 31.2.

Method B.—A mixture of 6.6 g. (0.05 mole) of 1,1,3-tricyano-2-aminopropene-1(malononitrile dimer), 6.0 g. (0.055 mole) of phenylhydrazine and 60 ml. of ethanol was heated under reflux for 2 hours. During this time copious ammonia evolution occurred. The reaction mixture was then thoroughly chilled and filtered to give 6.5 g. (58%) of pale red crystals. Recrystallization from ethanol with the addition of charcoal yielded white needles, m.p. 165–166°, identical in all respects with the product formed by method A above.

1-Phenyl-3-carboxymethyl-4-carboxamido-5-aminopyrazole (VII).—A mixture of 2.23 g. of 1-phenyl-3-cyanomethyl-4-cyano-5-aminopyrazole, 0.8 g. of sodium hydroxide and 15 ml. of water was heated under reflux for 6 hours, by which time ammonia evolution had almost ceased. Complete solution was achieved after 10–15 minutes. The hot reaction solution was acidified to *p*H 5–6 with glacial acetic acid and a solution of 2.3 g. of lead acetate trihydrate dissolved in 20 ml. of water added. The resulting mixture was cooled and the precipitated lead salt collected by filtration and washed well with water. It was then suspended in 60 ml. of boiling water and a stream of hydrogen sulfide passed through the suspension until it was saturated. The precipitated lead sulfide was filtered hot, the filtrate treated with charcoal and again filtered, and the filtrate allowed to cool. White crystals separated which were collected by filtration and dried. A small second crop was obtained by concentration of the mother liquor to give a total yield of 1.4 g. (54%). Recrystallization from water yielded white platelets, m.p. 193° dec.

Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.4; H, 4.7; N, 21.5. Found: C, 55.6; H, 4.7; N, 21.4.

1-Phenyl-3-carbethoxymethyl-4-cyano-5-aminopyrazole (X).—A mixture of 22.3 g. of 1-phenyl-3-cyanomethyl-4-cyano-5-aminopyrazole, 200 ml. of anhydrous dioxane and 25 ml. of absolute ethanol was warmed gently until complete solution had taken place. Through this solution was passed a stream of anhydrous hydrogen chloride at such a rate that the temperature of the reaction mixture never rose above 30°. After 1–2 hours a white, crystalline solid started to separate out. Hydrogen chloride was passed through the solution for a total of 4–5 hours (to complete saturation) and the reaction mixture allowed to stand overnight at 0°. (It was necessary to maintain anhydrous conditions throughout these operations because the imino ether hydrochloride which was formed was extremely hygroscopic and rapidly decomposed under the reaction conditions in the presence of moisture to give a yellow solution.) The white solid was collected by filtration, washed carefully with a small amount of absolute ether and stored in a desiccator over potassium hydroxide.

The imino ether hydrochloride prepared as described above was dissolved in 200–300 ml. of cold water, whereupon rapid hydrolysis took place with the separation of a white crystalline precipitate. In order to ensure complete hydrolysis, the reaction mixture was heated to 60° for 10 minutes. It was then cooled and filtered to yield 24.0 g. (89%) of crude ester, which was recrystallized from a small amount of ethanol to give stout colorless prisms, m.p. 109–110°.

Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.2; H, 5.2; N, 20.7. Found: C, 62.3; H, 5.3; N, 20.9.

1-Phenyl-3-carboxymethyl-4-cyano-5-aminopyrazole (XI).—A suspension of 5.4 g. of 1-phenyl-3-carbethoxymethyl-4-cyano-5-aminopyrazole in a solution of 7.0 g. of sodium carbonate monohydrate in 70 ml. of water was stirred and heated on a boiling water-bath until complete solution had been achieved (30 minutes). The reaction mixture was then chilled to 0°, acidified with concentrated hydrochloric acid, and the precipitated white solid collected by filtration and washed well with water: yield, 4.8 g. The product recrystallized from water to give 4.05 g. (84%) of long white needles, m.p. 170–172° with effervescence. The melt then partially resolidified and remelted between 250–260°.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.5; H, 4.2; N, 23.1. Found: C, 59.6; H, 4.2; N, 23.2.

2-Phenyl-3-amino-4,6-dihydroxypyrazolo(4,3-c)pyridine (VIII). Method A.—A suspension of 1.0 g. of 1-phenyl-3-cyanomethyl-4-cyano-5-aminopyrazole in 10 ml. of concentrated hydrochloric acid was heated under reflux for 20 minutes to give a clear yellow solution. Addition of 10 ml. of cold water followed by slow cooling resulted in the separation of yellow crystals which were collected by filtration and washed with water. Concentration of the mother liquor under reduced pressure yielded a second crop of crystals to give a total yield of 0.95 g. (87%). Recrystallization from water yielded either yellow platelets or long yellow needles, m.p. 266–267°; $\lambda_{max}^{H_2O}$ 246, 280 (shoulder), mμ; log ε 4.15, 3.80.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.5; H, 4.2; N, 23.1. Found: C, 59.5; H, 4.2; N, 23.5.

Method B.—Under the same conditions, 1-phenyl-3-carboxymethyl-4-carboxamido-5-aminopyrazole was converted to VIII in 91% yield.

Method C.—One half gram of 1-phenyl-3-carboxymethyl-4-cyano-5-aminopyrazole was heated in a sublimation tube at 180° for 10 minutes. Under these conditions the material partially melted with decomposition and effervescence. The tube was then attached to a vacuum-pump and the contents sublimed at 180° (0.05 mm.). Two additional sublimations of the initial sublimate yielded 0.2 g. (40%) of dense yellow crystals, m.p. 266–267°.

The products formed by methods A, B and C were all shown to be identical by mixture melting point determinations and by comparison of infrared spectra.

1-Phenyl-3-carboxymethyl-5-aminopyrazole (XIII).—A mixture of 6.7 g. of 1-phenyl-3-cyanomethyl-4-cyano-5-aminopyrazole, 18.0 g. of sodium hydroxide and 60 ml. of water was heated under reflux until ammonia evolution ceased (approximately 10 hours.) During this time the starting material gradually went into solution. The cold reaction solution was diluted with 60 ml. of water, adjusted to *p*H 6–7 with glacial acetic acid and an excess of saturated mercuric acetate solution added. The white mercury salt which separated was collected by filtration, washed thoroughly with ice-water and suspended in 100 ml. of boiling water. Through this suspension was passed a stream of hydrogen sulfide until complete saturation had been achieved (10 minutes). The precipitated mercuric sulfide was filtered off hot, the filtrate treated with charcoal and cooled to yield 3.7 g. (57%) of white crystals. Recrystallization from water yielded white needles, m.p. 180–182° dec.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.8; H, 5.1; N, 19.3. Found: C, 61.1; H, 5.4; N, 18.8.

1-Phenyl-3-methyl-5-aminopyrazole (XIV). Method A.—One-half gram of 1-phenyl-3-carboxymethyl-5-aminopyrazole was heated for 10 minutes in a sublimation tube at 200°. The material melted with evolution of carbon dioxide. The tube was then attached to a vacuum-pump and the decar-

(23) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J., and Drs. G. Weiler and F. B. Strauss, Oxford, England. All melting points are corrected.

boxylated product sublimed at 200° (0.05 mm.) to give 0.24 g. (60%) of a colorless liquid sublimate which rapidly solidified; m.p. 114–116°.

Method B.—A mixture of 1.98 g. of 1-phenyl-3-methyl-4-cyano-5-aminopyrazole,[7] 6.0 g. of sodium hydroxide and 20 ml. of water was heated under reflux for 14 hours until ammonia evolution had ceased. During this time the starting material gradually went into solution. The cooled reaction mixture was diluted with 30 ml. of water and extracted three times with 50-ml. portions of chloroform. The chloroform extracts were discarded, the aqueous phase was acidified to *p*H 4 with concentrated hydrochloric acid, and this acidified solution was extracted with three 50-ml. portions of chloroform. The combined extracts were dried over anhydrous magnesium sulfate, evaporated to dryness and the yellow residue sublimed at 180° (0.05 mm.) to give 0.7 g. (41%) of colorless crystals, m.p. 115–116°.

Method C.—This material was prepared from the phenylhydrazone of cyanoacetone by the method of Mohr.[8]

The products obtained by methods A, B and C were identical, as judged by mixture melting point determinations and by comparison of infrared spectra.

1-Methyl-3-cyanomethyl-4-cyano-5-aminopyrazole (XVIII). Method A.—To a boiling solution of 33.0 g. (0.5 mole) of malononitrile in 90 ml. of ethanol was added a solution of 11.5 g. (0.25 mole) of methylhydrazine in 15 ml. of ethanol at such a rate that the mixture continued to boil without external heating. After the addition of all of the methylhydrazine solution, the reaction mixture was heated under reflux for 15 minutes, thoroughly chilled at 0° and filtered to give 12.0 g. (30%) of crude product. Two recrystallizations from water with the aid of charcoal yielded long, white needles, m.p. 178°.

Anal. Calcd. for $C_7H_7N_5$: C, 52.2; H, 4.4; N, 43.5. Found: C, 52.5; H, 4.3; N, 43.0.

Method B.—To a boiling solution of 13.2 g. (0.1 mole) of 1,1,3-tricyano-2-aminopropene-1 (malononitrile dimer) in 100 ml. of ethanol was added a solution of 5.0 g. (0.11 mole) of methylhydrazine in 30 ml. of ethanol at such a rate that the reaction mixture continued to boil without external heating. After addition of all of the methylhydrazine, the reaction mixture was heated a further 30–45 minutes and then worked up as described above to give 9.5 g. (59%). One recrystallization from water with the use of charcoal yielded long, white needles, m.p. 178°.

The products obtained by methods A and B were identical as judged by a mixture melting point determination and by comparison of infrared spectra.

1-Methyl-3-carboxymethyl-4-carboxamido-5-aminopyrazole (XX).—A mixture of 4.85 g. of 1-methyl-3-cyanomethyl-4-cyano-5-aminopyrazole, 2.4 g. of sodium hydroxide and 30 ml. of water was heated under reflux for 5 hours until the evolution of ammonia had almost ceased. The hot reaction mixture was acidified to *p*H 5–6 with glacial acetic acid and a warm solution of 6.9 g. of lead acetate trihydrate in 60 ml. of water added. The reaction mixture was heated to boiling for a few minutes, the precipitated lead salt filtered off and washed well with ice-water. It was then suspended in 150 ml. of boiling water and hydrogen sulfide passed through the solution for 10 minutes until complete saturation resulted. The lead sulfide was removed by filtration from the hot suspension, and the filtrate was treated with charcoal and filtered. Slow cooling of the filtrate then yielded 2.95 g. (50%) of white crystals which were recrystallized from water to give white prisms or needles, m.p. 205° dec.

Anal. Calcd. for $C_7H_{10}N_4O_3$: C, 42.4; H, 5.1; N, 28.3. Found: C, 42.7; H, 5.1; N, 28.1.

2-Methyl-3-amino-4,6-dihydroxypyrazolo(4,3-c)pyridine (XXI).—A solution of 1.0 g. of 1-methyl-3-cyanomethyl-4-cyano-5-aminopyrazole in 15 ml. of concentrated hydrochloric acid was heated to boiling, whereupon a white crystalline solid started to separate out. After 10 minutes of refluxing, 15 ml. of water was added to the reaction mixture, which was then chilled and filtered to give 1.05 g. (94%). Recrystallization from water yielded light yellow needles, m.p. 326° dec.; $\lambda_{max}^{H_2O}$ 242, 279 mμ; log ε 3.76, 3.73.

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.7; H, 4.5; N, 31.1. Found: C, 46.4; H, 4.5; N, 31.3.

The same compound was obtained in 92% yield by treatment of 1-methyl-3-carboxymethyl-4-carboxamido-5-aminopyrazole with hydrochloric acid under the same conditions.

2-Methyl-3-amino-4-hydroxy-7-carboxypyrazolo(4,3-c)pyridine (XXII).—A mixture of 3.0 g. of 1-methyl-3-carboxymethyl-4-carboxamido-5-aminopyrazole, 45 ml. of ethyl orthoformate and 45 ml. of acetic anhydride was heated under reflux for 3 hours and then evaporated under reduced pressure. The residue was dissolved in 50 ml. of absolute ethanol and the solution again evaporated to dryness under reduced pressure. The red-brown residue was then dissolved in 20 ml. of 0.5 *N* sodium hydroxide, diluted with 200 ml. of water, boiled 5 minutes with charcoal and filtered. Acidification of the hot filtrate with glacial acetic acid to the point of turbidity followed by cooling caused the separation of 1.4 g. (44%) of a light orange-yellow precipitate which recrystallized from water to give very light yellow crystals, m.p. >350°; $\lambda_{max}^{0.1\ N\ NaOH}$ 227, 237–246 (shoulder), 284, 332 mμ; log ε 4.33, 4.19, 3.86, 4.00.

Anal. Calcd. for $C_8H_8N_4O_3$: C, 46.1; H, 3.9; N, 26.9. Found: C, 45.7; H, 3.8; N, 26.8.

2-Phenyl-3-amino-4-hydroxy-7-carboxypyrazolo(4,3-c)pyridine (XVII).—This compound was prepared in 94% yield from 1-phenyl-3-carboxymethyl-4-carboxamido-5-aminopyrazole and a mixture of ethyl orthoformate and acetic anhydride as described above. The crude product was recrystallized from aqueous ethanol to give a light yellow microcrystalline solid, m.p. >350°; $\lambda_{max}^{0.1\ N\ NaOH}$ 242, 277, 332 mμ; log ε 4.37, 4.12, 3.97.

Anal. Calcd. for $C_{13}H_{10}N_4O_3$: C, 57.8; H, 3.7; N, 20.7. Found: C, 57.5; H, 3.6; N, 20.5.

1-Methyl-3-carboxymethyl-5-aminopyrazole (XXIII).—A mixture of 6.5 g. of 1-methyl-3-cyanomethyl-4-cyano-5-aminopyrazole, 15 g. of sodium hydroxide and 50 ml. of water was heated under reflux until ammonia evolution had completely ceased (about 8 hours). Following the rapid solution of the pyrazole in the alkali, a yellow precipitate rapidly separated which then slowly dissolved as heating continued. The reaction was cooled, diluted with 50 ml. of water, adjusted to *p*H 6–7 with glacial acetic acid and treated with a saturated solution of mercuric acetate until no more precipitation occurred. The mercury salt was collected by filtration, washed with ice-water, suspended in 100 ml. of boiling water, and the mixture saturated with hydrogen sulfide. Removal of the mercuric sulfide followed by concentration of the decolorized filtrate under reduced pressure resulted in the separation of 4.4 g. (70%) of light red crystals which were recrystallized from aqueous dioxane (1:3) to give white needles, m.p. 202° dec.

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.4; H, 5.85; N, 27.1. Found: C, 46.4; H, 5.85; N, 27.1.

1,3-Dimethyl-5-aminopyrazole (XXIV). Method A.—A solution of 16.4 g. (0.2 mole) of β-aminocrotononitrile, 50 ml. of absolute ethanol and 12.0 g. (0.26 mole) of methylhydrazine was heated under reflux until ammonia evolution had ceased (about 12 hours). Evaporation of the reaction mixture under reduced pressure yielded a colorless residue which rapidly solidified; crude yield 21.5 g. (97%). Recrystallization from a small amount of benzene with the aid of charcoal yielded 16.6 g. (75%) of long white needles, m.p. 80–81°.

Anal. Calcd. for $C_5H_9N_3$: C, 54.0; H, 8.2; N, 37.8. Found: C, 53.7; H, 8.3; N, 38.0.

Method B.—One-half gram of 1-methyl-3-carboxymethyl-5-aminopyrazole was placed in a sublimation tube and heated for 10 minutes at 220°. The material rapidly melted with evolution of carbon dioxide. The tube was then connected to a vacuum-pump and the decarboxylated product sublimed at 220° (0.05 mm.) to give 0.18 g. (50%) of white crystals, m.p. 79–80°.

Method C.—A suspension of 2.72 g. of 1,3-dimethyl-4-cyano-5-aminopyrazole[7] in 20 ml. of water containing 6.0 g. of sodium hydroxide was heated under reflux until evolution of ammonia had ceased (about 8 hours). The pyrazole went slowly into solution during this time. One-half of the cooled reaction mixture was acidified to *p*H 5–5.5 with glacial acetic acid and an excess of saturated mercuric acetate solution added. A very small amount of a white solid separated which was collected by filtration, washed with ice-water, suspended in boiling water and treated with hydrogen sulfide in the usual manner. Evaporation of the filtrate after removal of the mercuric sulfide yielded no residue, indicating that essentially complete decarboxylation of the intermediate 1,3-dimethyl-4-carboxy-5-aminopyrazole had

taken place. The other half of the hydrolysis solution above was adjusted to *p*H 7–7.5 and a saturated mercuric acetate solution added dropwise, with the occasional addition of 4 *N* sodium hydroxide to maintain the *p*H at 7–7.5. The precipitated mercuric salt was worked up in the usual manner to give 0.3 g. of a white solid which sublimed at 100° (0.05 mm.) to give 0.24 g. (22%) of white needles, m.p. 79–81°.

The conversion of 1,3-dimethyl-4-cyano-5-aminopyrazole to XXIV could be carried out on a preparative scale as follows: A mixture of 10.9 g. of 1,3-dimethyl-4-cyano-5-aminopyrazole, 24 g. of sodium hydroxide and 80 ml. of water was heated under reflux for 8 hours. The reaction mixture was then cooled, acidified to *p*H 3–4 with concentrated hydrochloric acid, heated to boiling for 10 minutes to ensure complete decarboxylation and finally adjusted to *p*H 9–10 with sodium hydroxide. It was extracted with chloroform, the chloroform extracts dried and distilled and the crystalline residue (5.6 g., 63%) sublimed at 140° (0.05 mm.) to give white needles, m.p. 79–81°.

The products from methods A, B and C were all identical as shown by mixture melting point determinations and by comparison of infrared spectra.

1,3-Dimethyl-4-nitroso-5-aminopyrazole (XXVIII).—To a solution of 5.55 g. (0.05 mole) of 1,3-dimethyl-5-aminopyrazole in 50 ml. of water containing 7 ml. of glacial acetic acid, maintained at 5–8°, was added dropwise and with stirring over the course of one hour a solution of 4.0 g. (0.058 mole) of sodium nitrite in 20 ml. of water. The reaction mixture became deep red after the addition of the first drops of the sodium nitrite solution, and toward the end of the addition a reddish-brown solid started to separate. Stirring and chilling were continued for an additional hour after all the sodium nitrite had been added, and the precipitated solid was then collected by filtration and washed with ice-water: yield 4.2 g. (60%). Recrystallization from water yielded deep red crystals, m.p. 169–171°.

Anal. Calcd. for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 40.0. Found: C, 42.85; H, 5.9; N, 39.8.

1,3-Dimethyl-4-nitroso-5-pyrazolone (XXIX). Method A.—A solution of 5.6 g. (0.05 mole) of 1,3-dimethyl-5-pyrazolone in 50 ml. of water containing 7 ml. of glacial acetic acid was nitrosated in the usual way at 0–5° with 4.0 g. (0.058 mole) of sodium nitrite in 20 ml. of water to give 5.1 g. (72%) of a brilliant yellow solid. Recrystallization from carbon tetrachloride followed by sublimation yielded shining yellow-orange crystals, m.p. 144–145°.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.0; N, 29.8. Found: C, 42.3; H, 5.0; N, 30.2.

Method B.—A solution of 1.4 g. of 1,3-dimethyl-4-nitroso-5-aminopyrazole in 20 ml. of 10% sodium hydroxide was heated under reflux until ammonia evolution had ceased (about 4 hours). The cold reaction mixture was acidified with concentrated hydrochloric acid until the deep red color changed to orange and a yellow precipitate separated out (about *p*H 1–2). The mixture was then extracted with chloroform and the chloroform extracts were dried over magnesium sulfate and evaporated to dryness to give 1.05 g. (75%) of a brilliant yellow solid. Recrystallization from carbon tetrachloride yielded shining yellow-orange crystals, m.p. 144–145°.

The products formed by methods A and B were shown to be identical by a mixture melting point determination and by comparison of infrared spectra.

2-Methylsemicarbazide was prepared in excellent yield essentially according to a method described by v. Brüning.[24] However, since it has recently been claimed[25] that this method gives very poor yields, our procedure is given in detail.

To 1 l. of water was added 68.0 (0.5 mole) of potassium hydrogen sulfate, 40.5 g. (0.5 mole) of potassium cyanate and then 23.0 g. (0.5 mole) of methylhydrazine, care being taken that the temperature did not rise above 40°. The reaction solution was allowed to stand at room temperature overnight and was then evaporated under reduced pressure to dryness, care again being taken to keep the temperature below 40°. The residual crystals were dried in a vacuum oven at 40°, placed in a Soxhlet cup and extracted with absolute ethanol. Evaporation of the ethanol yielded 38.0 g. (85%) of white crystals, m.p. 117°, which were recrystallized from chloroform. The reported melting point for this compound is 113°[24] and 115°.[25]

2-Methylsemicarbazone of Ethyl Acetoacetate.—To a solution of 8.9 g. of 2-methylsemicarbazide in 30 ml. of water adjusted to *p*H 4 was added 14.3 g. of ethyl acetoacetate and the mixture was shaken for five minutes. Cooling yielded 17.4 g. (91%) of a white crystalline solid which was recrystallized from a mixture of ethanol and ethyl acetate to give white needles, m.p. 147–148°.

Anal. Calcd. for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.15; N, 20.9. Found: C, 47.9; H, 7.3; N, 21.0.

1,3-Dimethyl-5-pyrazolone (XXX).—One and nine-tenths grams of the 2-methylsemicarbazone of ethyl acetoacetate contained in a 25-ml. erlenmeyer flask was heated for 8 minutes in an oil-bath at 200°. The material melted to a colorless liquid which rapidly turned yellow and then reddish-brown, with gas evolution. The sirup thus obtained was dissolved in 10 ml. of water, whereupon a small amount of a white solid separated out. This was collected by filtration and discarded, and the filtrate was extracted thoroughly with chloroform. Evaporation of the chloroform extracts to dryness yielded a reddish-brown, partially solid residue which was transferred to a sublimation tube and sublimed at 105° (0.05 mm.) to give 0.22 g. of a white, crystalline solid, m.p. 90–100°. Two further sublimations yielded white crystals, m.p. 117°.

This material was identical with a sample of 1,3-dimethyl-5-pyrazolone prepared from ethyl acetoacetate and methylhydrazine according to the method of Knorr[16] and of v. Auwers and Niemeyer.[18]

1-Phenyl-3-cyanomethyl-4-cyano-5-ethoxalylaminopyrazole (XXXII).—A solution of 0.5 g. (0.0125 mole) of potassium in 30 ml. of absolute ethanol containing 2.0 g. (0.0137 mole) of diethyl oxalate was stirred for 10 minutes at room temperature and then treated with 2.23 g. (0.01 mole) of finely powdered 1-phenyl-3-cyanomethyl-4-cyano-5-aminopyrazole. A light yellow precipitate rapidly separated. After 1.5 hours of stirring, the reaction mixture was filtered and the collected solid (3.4 g.) dissolved in 50 ml. of water. Acidification with glacial acetic acid resulted in the separation of 2.9 g. (90%) of a solid which was recrystallized from ethanol to give colorless needles, m.p. 138°.

Anal. Calcd. for $C_{16}H_{13}N_5O_3$: C, 59.4; H, 4.05; N, 21.7. Found: C, 59.5; H, 4.0; N, 21.9.

1-Phenyl-3-cyanomethyl-4-cyano-5-carbethoxymethoxymethyleneaminopyrazole (XXXIII).—To a solution of 3.23 g. of 1-phenyl-3-cyanomethyl-4-cyano-5-ethoxalylaminopyrazole in 25 ml. of tetrahydrofuran was added 20 ml. of an ether solution of diazomethane prepared from 2.1 g. (~ 0.02 mole) of nitrosomethylurea. The reaction mixture was allowed to stand overnight at 0° and then the solvents were removed by distillation under reduced pressure. The residual yellow oil was dissolved in a small quantity of ethanol and the solution treated with charcoal, filtered, and the filtrate chilled to 0°. After 1.5 days, crystallization commenced; yield 1.75 g. (52%). Recrystallization from ethanol yielded colorless needles, m.p. 75–76°.

Anal. Calcd. for $C_{17}H_{15}N_5O_3$: C, 60.5; H, 4.5; N, 20.8. Found: C, 60.8; H, 4.5; N, 21.2.

1-Phenyl-3-cyanomethyl-4-amino-6-carbethoxypyrazolo(3,4-d)pyrimidine (XXXIV).—A solution of 1.69 g. of 1-phenyl-3-cyanomethyl-4-cyano-5-carbethoxymethoxymethyleneaminopyrazole in 10 ml. of tetrahydrofuran containing 1 ml. of ethanol saturated (at 0°) with ammonia was allowed to stand 2 hours at room temperature. The white crystalline solid which separated was collected by filtration and washed with cold ethanol; yield 1.3 g. (81%). Recrystallization from nitromethane containing a small amount of dimethylformamide yielded white needles, m.p. 265–275°. The melting point behavior of this compound was more a gradual decomposition to a reddish-brown liquid than a true melting or decomposition point; λ_{max}^{EtOH} 241, 315 mμ; log ε 4.51, 3.91.

Anal. Calcd. for $C_{16}H_{14}N_6O_2$: C, 59.6; H, 4.4; N, 26.1. Found: C, 59.4; H, 4.3; N, 26.3.

1-Phenyl-3-methyl-4-aminopyrazolo(3,4-d)pyrimidine (XXXV).—A solution of 2.0 g. of 1-phenyl-3-methyl-4-cyano-5-aminopyrazole[7] in 10 ml. of formamide was heated under reflux for 1 hour. Cooling caused the separation of a gray precipitate. The reaction mixture was diluted with 30 ml. of water, filtered, the collected solid washed thor-

(24) G. v. Brüning, *Ann.*, **253**, 5 (1889).

(25) C. Vogelesang, *Rec. trav. chim.*, **62**, 5 (1943).

oughly with water and recrystallized from aqueous ethanol to give 1.55 g. (68%) of white crystals, m.p. 184–185°; λ_{max}^{EtOH} 240, 291 mμ; log ε 4.56, 4.04.

Anal. Calcd. for $C_{12}H_{11}N_5$: C, 64.0; H, 4.9; N, 31.1. Found: C, 64.0; H, 5.0; N, 31.0.

1-Methyl-3-cyanomethyl-4-amino-6-carbethoxypyrazolo(3,4-d)pyrimidine (XXXIX).—A solution of 2.5 g. (0.0625 mole) of potassium in 100 ml. of absolute ethanol containing 10.0 g. (0.0685 mole) of diethyl oxalate was stirred for 10 minutes and then treated with 8.1 g. (0.05 mole) of finely powdered 1-methyl-3-cyanomethyl-4-cyano-5-aminopyrazole. After a few minutes a white, crystalline solid separated from the yellow reaction mixture. After one hour of stirring, this solid (12.25 g.) was collected by filtration and washed well with ethanol. Three grams of this potassium salt was dissolved in 15 ml. of water, 30 ml. of chloroform added, the mixture transferred to a separatory funnel, and 5% hydrochloric acid added dropwise until further addition of acid no longer caused the separation of an oily precipitate in the aqueous phase. The chloroform layer was drawn off, the aqueous layer re-extracted with 10 ml. of chloroform, and the combined extracts dried over magnesium sulfate and evaporated to dryness.

The residual sirup was dissolved in 30 ml. of tetrahydrofuran and 20 ml. of an ether solution of diazomethane (from 2.1 g. of nitrosomethylurea) added. The reaction mixture was allowed to stand at 0° overnight and was then treated with 2 ml. of ethanol saturated (at 0°) with ammonia. After two hours of stirring at room temperature, the precipitated solid (1.55 g., 48%) was collected by filtration and recrystallized from nitromethane to give white needles, m.p. 246° dec.; λ_{max}^{EtOH} 260, 303 mμ; log ε 3.84, 3.74.

Anal. Calcd. for $C_{11}H_{12}N_6O_2$: C, 50.8; H, 4.65; N, 32.3. Found: C, 50.9; H, 5.0; N, 32.0.

1-Phenyl-3-cyanomethyl-4-cyano-5-ethoxymethyleneaminopyrazole (XLI).—To 50 ml. of an equimolar mixture of acetic anhydride and ethyl orthoformate (which had been allowed to stand for five days) was added 22.3 g. of 1-phenyl-3-cyanomethyl-4-cyano-5-aminopyrazole, and the mixture was heated at 140° in an oil-bath for 3 hours. The reaction flask was fitted with a short air condenser so that the majority of the ethyl acetate which was formed during the reaction distilled off during the heating period. The red-brown solution was evaporated under reduced pressure, the residue dissolved in 50 ml. of ethanol and the solution again concentrated. This process was repeated several times, and the red-brown, oily residue was then cooled to 0°. It rapidly solidified upon scratching. Recrystallization from ethanol with the use of charcoal yielded 26.0 g. (93%) of pearl-colored platelets, m.p. 86°.

Anal. Calcd. for $C_{15}H_{13}N_5O$: C, 64.5; H, 4.7; N, 25.1. Found: C, 64.4; H, 4.6; N, 25.1.

1-Phenyl-3-cyanomethyl-4-aminopyrazolo(3,4-d)pyrimidine (XLII). Method A.—A suspension of 2.8 g. of 1-phenyl-3-cyanomethyl-4-cyano-5-ethoxymethyleneaminopyrazole in 20 ml. of absolute ethanol containing 2 ml. of ethanol saturated (at 0°) with ammonia was stirred at room temperature for 2 hours. The starting material rapidly dissolved, and after a short time a light yellow solid started to separate out. The reaction mixture was cooled and filtered to give 2.35 g. (94%) of almost colorless product. Recrystallization from ethanol yielded white needles and platelets, m.p. 241–243° (to a reddish-brown liquid); λ_{max}^{EtOH} 238, 291 mμ; log ε 4.50, 4.09.

Anal. Calcd. for $C_{13}H_{10}N_6$: C, 62.4; H, 4.0; N, 33.6. Found: C, 62.8; H, 3.9; N, 33.9.

Method B.—To a solution of 0.27 g. of sodium in 20 ml. of absolute ethanol was added 1.47 g. of finely powdered guanidine nitrate, and the mixture was stirred at room temperature for 1 hour. The precipitated sodium nitrate was removed by filtration and the filtrate was treated with 2.80 g. of 1-phenyl-3-cyanomethyl-4-cyano-5-ethoxymethyleneaminopyrazole. The pyrazole rapidly dissolved, and after a short time a light yellow solid separated out. After two hours of stirring, the reaction mixture was filtered to give 1.50 g. (60%) of almost colorless product. Recrystallization from ethanol yielded white platelets, m.p. 241–243°.

The products obtained by methods A and B were shown to be identical by a mixture melting point determination and by comparison of infrared spectra.

1-Phenyl-3-cyanomethyl-4-imino-5-amino-4,5-dihydropyrazolo(3,4-d)pyrimidine (XLIV).—A mixture of 28 g. of 1-phenyl-3-cyanomethyl-4-cyano-5-ethoxymethyleneaminopyrazole, 6.4 g of 98% hydrazine hydrate and 200 ml. of ethanol was stirred at room temperature for 1.5 hours. The initially clear solution rapidly deposited a tan crystalline solid as the reaction proceeded. Filtration yielded 24.0 g. (90%) which was recrystallized from ethanol to give light tan needles, m.p. 194–195°.

Anal. Calcd. for $C_{13}H_{11}N_7$: C, 58.9; H, 4.2; N, 37.0. Found: C, 58.9; H, 4.4; N, 37.0.

1-Phenyl-3-cyanomethyl-4-imino-5-(*n*-butyl)-4,5-dihydropyrazolo(3,4-d)pyrimidine (XLV).—To a solution of 0.73 g. (0.01 mole) of *n*-butylamine in 10 ml. of absolute ethanol was added, with stirring and at room temperature, 1.4 g. (0.005 mole) of 1-phenyl-3-cyanomethyl-4-cyano-5-ethoxymethyleneaminopyrazole. The pyrazole rapidly dissolved, and after about 5 minutes a white, crystalline precipitate started to separate out. The reaction mixture was stirred for an additional hour and then filtered to give 1.32 g. (86%). Recrystallization from ethanol yielded white needles, m.p. 115°; λ_{max}^{EtOH} 242, 283 mμ; log ε 4.36, 3.98.

Anal. Calcd. for $C_{17}H_{18}N_6$: C, 66.6; H, 5.9; N, 27.4. Found: C, 66.7; H, 6.0; N, 27.1.

1-Methyl-3-cyanomethyl-4-cyano-5-ethoxymethyleneaminopyrazole (XLVI) was prepared in 85% yield from 1-methyl-3-cyanomethyl-4-cyano-5-aminopyrazole and a mixture of ethyl orthoformate and acetic anhydride as described above under the preparation of XLI. Recrystallization from ethanol yielded small, white needles, m.p. 68–69°.

Anal. Calcd. for $C_{10}H_{11}N_5O$: C, 55.3; H, 5.1; N, 32.2. Found: C, 55.1; H, 5.2; N, 32.2.

1-Methyl-3-cyanomethyl-4-aminopyrazolo(3,4-d)pyrimidine(XLVII).—To 20 ml. of absolute ethanol containing 2 ml. of ethanol saturated (at 0°) with ammonia was added, with stirring, 2.17 g. of 1-methyl-3-cyanomethyl-4-cyano-5-ethoxymethyleneaminopyrazole. The starting material rapidly dissolved and after a short time a white solid separated out. The reaction mixture was stirred for 2 hours at room temperature and was then filtered to give 1.75 g. (93%). Recrystallization from ethanol yielded gleaming white platelets, m.p. 239–241° (to a red-brown liquid); λ_{max}^{EtOH} 260, 281 mμ; log ε 3.88, 3.95.

Anal. Calcd. for $C_8H_8N_6$: C, 51.05; H, 4.3; N, 44.7. Found: C, 51.2; H, 4.1; N, 44.9.

1-Methyl-3-cyanomethyl-4-imino-5-amino-4,5-dihydropyrazolo(3,4-d)pyrimidine (XLVIII).—To a solution of 0.64 g. (~0.02 mole) of 98% hydrazine in 20 ml. of absolute ethanol was added with stirring 2.17 g. (0.01 mole) of finely powdered 1-methyl-3-cyanomethyl-4-cyano-5-ethoxymethyleneaminopyrazole. A white solid immediately separated from the reaction mixture, which was stirred for 1 hour at room temperature and then filtered to give 1.90 g. (94%). The material was recrystallized from aqueous methanol (1:9), but the hot solution had to be rapidly cooled to avoid slow decomposition of the product which took place in hot solvents. The product was obtained in the form of white needles, m.p. 205° dec.; λ_{max}^{EtOH} 265 (shoulder) 268, 285 mμ; log ε 3.73, 3.74, 3.66.

Anal. Calcd. for $C_8H_9N_7$: C, 47.3; H, 4.5; N, 48.25. Found: C, 47.2; H, 4.6; N, 48.4.

1-Methyl-3-cyanomethyl-4-imino-5-(*n*-butyl)-4,5-dihydropyrazolo(3,4-d)pyrimidine (XLIV).—To a solution of 5.5 g. of *n*-butylamine in 70 ml. of ethanol was added with stirring a solution of 8.0 g. of 1-methyl-3-cyanomethyl-4-cyano-5-ethoxymethyleneaminopyrazole in 30 ml. of water. Cooling caused the separation of 7.8 g. (87%) of white needles, m.p. 104–106°, which were recrystallized from carbon tetrachloride.

Anal. Calcd. for $C_{12}H_{16}N_6$: C, 59.0; H, 6.6; N, 34.4. Found: C, 58.9; H, 6.5; N, 34.5.

1-Methyl-3-(2-aminoethyl)-4-aminopyrazolo(3,4-d)pyrimidine (L).—A suspension of 5.0 g. of 1-methyl-3-cyanomethyl-4-aminopyrazolo(3,4-d)pyrimidine and 3 g. of Raney nickel catalyst in 100 ml. of ethanol saturated (at 0°) with ammonia was hydrogenated at 110° and 130–140 atmospheres of hydrogen for 4 hours. The cooled reduction mixture was filtered from the catalyst, the filtrate was boiled for a few minutes with charcoal and again filtered, and the now colorless filtrate was evaporated to dryness under re-

duced pressure. Sublimation of the residue at 150° (0.05 mm.) yielded 3.2 g. (63%) of white needles, m.p. 163–165°. Recrystallization from water yielded a hydrate which decomposed on heating above 100°.

Anal. Calcd. for $C_8H_{12}N_6$: C, 50.0; H, 6.3; N, 43.5. Found: C, 50.0; H, 6.3; N, 43.5.

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Pteridines. XVII. Reactions of 2,4,6,7-Tetrachloropteridine. The Synthesis of 5,6,7,8-Tetrahydropteridine[1]

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A procedure suitable for the preparation of large quantities of 2,4,6,7-tetrahydroxypteridine (I) is given. Lithium aluminum hydride reduction of 2,4,6,7-tetrachloropteridine (II), prepared from I by chlorination, yields 2,4-dichloro-5,6,7,8-tetrahydropteridine (III), which upon catalytic reduction gives 5,6,7,8-tetrahydropteridine (XI). The structures of these reduction products are independently established. Reasons for the stability of III and XI, in contrast to the instability of 2,4-dichloropteridine (V) and pteridine (XII), and the failure of attempts to dehydrogenate XI to XII, are discussed. Catalytic reduction of 2,4,6,7-tetrachloropteridine yields a purple solid which is rapidly converted in the presence of air to 2,4-dichloro-6-hydroxy-7,8-dihydropteridine (VIII), whose structure is established by an independent synthesis and by further reduction to 6-hydroxy-7,8-dihydropteridine (X). Amination of III yields 2,4-diamino-5,6,7,8-tetrahydropteridine (XIII), which is readily oxidized through 2,4-diaminodihydropteridine (XIV) to 2,4-diaminopteridine (XV). Sodium borohydride reduction of XV in dimethylformamide solution yields XIV. Amination of II under strenuous conditions yields 2,4,6,7-tetraminopteridine (XVII) hydrochloride, which condenses with alloxan, oxalic acid and formamide to give 2,4-diamino-7,9-dihydroxypteridyl(6,7-g)pteridine (XIX), 2-amino-4,7,8-trihydroxypyrazino(2,3-g)pteridine (XX) and a formyl derivative of 2,4-diaminoimidazo(4,5-g)pteridine (XXI), respectively.

Although 2,4,6,7-tetrachloropteridine (II) has been known since 1941,[4] relatively little has been reported concerning its chemical reactivity or its use in pteridine synthesis. This compound was prepared by Schöpf[4] by the chlorination of 2,4,6,7-tetrahydroxypteridine (I) with a mixture of phosphorus pentachloride and phosphorus oxychloride. It was demonstrated that II could be partially hydrolyzed in wet ether solution or in warm 0.75 *N* sodium hydroxide to a dichlorodihydroxypteridine which was assumed to be 2,4-dichloro-6,7-dihydroxypteridine, and that it could be converted to I by heating at 140° for six and one-half hours in 25% sodium hydroxide. Schöpf further demonstrated in a preliminary experiment that partial amination of II took place under very mild conditions, although the product of the amination was not determined. More recently, Cain and Schenker[5,6] have found that all of the chlorine atoms of II may be replaced by alkylamino groups under sufficiently strenuous conditions, and the order of replacement of the chlorine atoms has been determined. No further reactions of II have been reported.

2,4,6,7-Tetrachloropteridine (II) thus appeared to be an accessible, reactive intermediate amenable to use in further pteridine syntheses, and the present communication presents the results of our further investigations with this compound. However, since relatively large amounts of II were desired, it was found necessary to re-examine the existing methods for the preparation of 2,4,6,7-tetrahydroxypteridine (I), its immediate precursor.

The first preparation of I, which may be regarded as the pteridine analog of uric acid, was reported by Wieland[7] and involved nitrous acid hydrolysis of the 2-amino group of leucopterin (2-amino-4,6,7-trihydroxypteridine). Purrmann[8] later described a direct synthesis of I by the fusion of 2,4-dihydroxy-5,6-diaminopyrimidine with oxalic acid under reduced pressure. Several minor modifications of this condensation have since been reported which utilize the pyrimidine sulfate with[4] and without[9] the addition of sodium acetate. Although these methods give satisfactory yields of I in small-scale preparations, attempts to scale up the reaction to preparative amounts have resulted, in our hands, in drastically lower yields. As a result, we have described in the Experimental section a further modification of this condensation which involves fusion of the hydrochloride salt of 2,4-dihydroxy-5,6-diaminopyrimidine with oxalic acid, and which gives consistently satisfactory yields of I in large-scale runs.

2,4,6,7-Tetrachloropteridine (II) was then prepared from I by previously described procedures,[4] except that the product was best purified by vacuum sublimation rather than by recrystallization. Reduction of II in ether or tetrahydrofuran solution with lithium aluminum hydride yielded a dichlorotetrahydropteridine in almost quantitative yield. This product was assigned the structure 2,4-dichloro-5,6,7,8-tetrahydropteridine (III) on the basis of the following evidence: (1) The ultraviolet absorption spectrum of III is similar to that given by 2,4-dichloro-5,6-diaminopyrimidine, except that the position of maximum absorption is shifted to longer wave lengths by 18 mμ. A bathochromic shift of similar magnitude was observed in com-

(1) For the previous paper in this series, see E. C. Taylor, J. W. Barton and T. S. Osdene, THIS JOURNAL, **80**, 421 (1958).

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