was washed with 5% sodium bicarbonate, dried, and evaporated *in vacuo*. The oil crystallized on standing in an ice bath, affording 0.83 g. (31% yield) of methyl ester **14**. Recrystallization from petroleum ether afforded colorless crystals: m.p. 49–50° (raised to 52–53.5° by repeated crystallization); infrared (CCl_4), 5.69, 5.87, and a doublet at 6.00 and 6.14 μ. See the corresponding ethyl ester **16** described below.

Anal. Calcd. for $C_{12}H_{11}O_3Br$: C, 50.90; H, 3.92; Br, 28.23. Found: C, 51.31; H, 4.43; Br, 26.87.

1-Methyl-2-carboxy-7-bromo-3,4-dihydronaphthalene (7 Br).—To an ice-cold solution of methylmagnesium iodide, prepared from 1.87 g. (0.078 g.-atom) of magnesium and 14.63 ml. (0.234 mole) of iodomethane in dry tetrahydrofuran (THF), was added a cold solution of keto acid **13** in dry THF. The mixture was stirred for 2 hr. at 0°, allowed to warm to room temperature over a period of 3 hr., and then refluxed for 45 min. The mixture was cooled to 0–3°, decomposed with cold, dilute hydrochloric acid, and the THF was removed by distillation (maximum distillate b.p. *ca.* 100°). The resulting aqueous solution was extracted with ether which in turn was washed with 5% sodium bicarbonate. After acidification of these bicarbonate washings, the acidic products were obtained by extraction with ether which was dried (Norit) and evaporated *in vacuo*. The resulting solid was recrystallized from benzene, affording minute quantities (*ca.* 3–5 mg.) of white needles, m.p. 214.5–215° (evolution of gas).[20]

Ethyl 7-Bromo-1-tetralone-2-glyoxalate (15).—To a cold, fresh solution of sodium ethoxide (prepared from 3.4 g. (0.147 g.-atom) of sodium in *ca.* 30 ml. of dry ethanol) was added over a period of 15 min. with stirring, a warm solution of 24.8 g. (0.110 mole) of 7-bromo-1-tetralone (**12**) and 16.4 g. (0.112 mole) of diethyl oxalate in 30 ml. of dry ethanol. The mixture was stirred in an ice–water bath for 1 hr. and for an additional 6 hr. at room temperature. Cold, dilute sulfuric acid was then added and the mixture was allowed to stand overnight. The dark, tacky solid was collected, dissolved in ether (Norit), dried, and concentrated, affording 26.70 g. (72.5% yield) of oxalyl ester **15** as bright yellow crystals: m.p. 63–65°[21]; infrared (CCl_4), 5.75 (C=O), and 6.11, 6.28, and 6.50 μ (C=C).[22]

Anal. Calcd. for $C_{14}H_{13}O_4Br$: C, 51.71; H, 4.03; Br, 24.58. Found: C, 51.67; H, 4.15; Br, 24.33.

Ethyl 7-Bromo-1-tetralone-2-carboxylate (16).—The decarbonylation was carried out by heating 25.43 g. (0.078 mole) of oxalyl ester **15** with 2 g. of powdered soft glass at 180–185° at 40 mm. When the vigorous evolution had ceased (*ca.* 30 min.) the pressure was lowered to 0.75 mm. and the fraction distilling at 155–170° was collected, affording 20.35 g. (88% yield) of ethyl 7-bromo-1-tetralone-2-carboxylate (**16**). This was recrystallized from 95% ethanol affording colorless crystals, m.p. 63–66.5°.[23]

Anal. Calcd. for $C_{13}H_{13}O_3Br$: C, 52.54; H, 4.41; Br, 26.89. Found: C, 52.87, 52.62; H, 4.41, 4.71; Br, 27.33, 26.63.

The infrared spectra of **16** (CCl_4) had peaks at 5.77, 5.93, and a doublet at 6.08 and 6.17 μ,. Ethyl 1-tetralone-2-carboxylate is reported also to absorb at 5.77, 5.89, and 6.08 μ, corresponding to the ester carbonyl, the unsaturated keto carbonyl, and the chelated ester, respectively.[24] The methyl ester shows similar absorption (*vide supra*). N.m.r. ($CDCl_3$) showed peaks at τ −2.45 (singlet, enol-OH), τ 2.03 (singlet C_8-H),[25] τ 2.53–3.02 (complex multiplet, Ar-H), τ 5.67 (quartet, $-CO_2CH_2CH_3$), τ 7.32 (unresolved multiplet, may be doublet or triplet, $-CH_2-CH_2-$), and τ 8.63 (triplet, $-CO_2CH_2-CH_3$).

Attempted Preparation of 1-Methyl-2-carbethoxy-7-bromo-3,4-dihydronaphthalene (8b Br).—Methylmagnesium iodide in dry ether was added to a solution of β-keto ester **16** in cold ether. Gas evolution was apparent immediately, and careful work-up in the usual manner afforded 2.28 g. (77% recovery) of starting material. No further attempts were made to effect this conversion.

(20) A sample of this α,β-unsaturated acid prepared by the lengthy independent synthesis above melts at 215–215.5° with *no observable gas evolution*. It is believed that the procedure here affords a compound containing an appreciable amount of the original keto acid.

(21) Attempts were made to prepare the *p*-nitrophenylhydrazine derivative, but elemental analyses could not be reconciled with a reasonable structure for the red solid, m.p. 178–179°. The approximate formulation is $C_{22}H_{18}BrN_3O_5$.

(22) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 142.

(23) This compound crystallized from ether in both rods and plates, but these were shown to be identical by mixture melting point. This appears to be solely a nucleation phenomenon.

(24) L. J. Bellamy and R. F. Brance, *J. Chem. Soc.*, 4487 (1954).

(25) In the n.m.r. spectra of all naphthalene compounds containing a *peri*-hydrogen *ortho* to a halogen atom, we find a distinct separation of this proton from the remainder of the aromatic ones.

The Synthesis of 4-Aminoisoxazolo[5,4-*d*]pyrimidines[1]

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A number of derivatives of isoxazolo[5,4-*d*]pyrimidine have been prepared as potential purine antagonists. Condensation of hydroxylamine with methylethoxymethylenemalononitrile, ethylethoxymethylenemalononitrile, and phenylmethoxymethylenemalononitrile gave a series of 3-substituted 4-cyano-5-aminoisoxazoles which, upon reaction with ethyl orthoformate–acetic anhydride, followed by an amine, gave 4-amino- and substituted aminoisoxazolo[5,4-*d*]pyrimidines. The structures of several of the 4-substituted amino derivatives were confirmed through independent synthesis by heating the 4-amino derivative with a mixture of the alkyl amine and its hydrochloride salt. Catalytic reduction of the 4-aminoisoxazolo[5,4-*d*]pyrimidines resulted in cleavage of the O–N bond; hydrolysis of the resulting imine then gave 4-amino-5-acetyl- and 5-benzoyl-6-hydroxypyrimidines. Several derivatives of the pyrido[2,3-*d*]pyrimidine ring system were prepared by subsequent reaction with malononitrile.

There is continuing interest in the preparation of potential purine antagonists for studies in cancer chemotherapy, since many of the currently active purine derivatives and analogs exhibit excessive toxicity and are unsuited for clinical use. One may cite as an example 4-aminopyrazolo[3,4-*d*]pyrimidine, which, although active as a purine antimetabolite, shows signs of hepatotoxicity in man.[2] Many derivatives of 4-aminopyrazolo[3,4-*d*]pyrimidine (and related purine analogs) have been prepared in an attempt to improve the antitumor activity and reduce the toxicity of the parent compound.[3] We wish to describe in this paper the synthesis and chemical properties of some derivatives of the little-known, structurally related isoxazolo[5,4-*d*]pyrimidine ring system.

The preparation of a bicyclic ring system, such as the desired isoxazolo[5,4-*d*]pyrimidine system, can be approached from either of two directions; that is, the

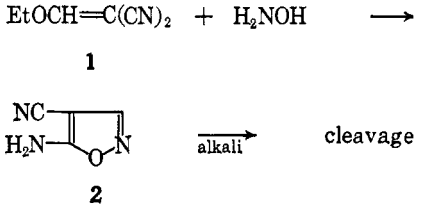
(1) This work was supported by a research grant (CY-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) R. K. Shaw, R. N. Shulman, J. D. Davidson, D. P. Rall, and E. Frei, *Cancer*, **13**, 482 (1960).

(3) See E. Y. Sutcliffe, K. Y. Zee-Cheng, C. C. Cheng, and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 588 (1962), and preceding papers cited therein.

pyrimidine ring can be formed first and the isoxazole ring closed in the terminal step of the synthetic sequence, or the isoxazole ring can be prepared initially and the pyrimidine ring attached in the terminal stages. We chose the latter approach because of prior experience in the cyclization of *o*-aminonitriles to condensed 4-aminopyrimidine systems. This work has been described in detail elsewhere.[4]

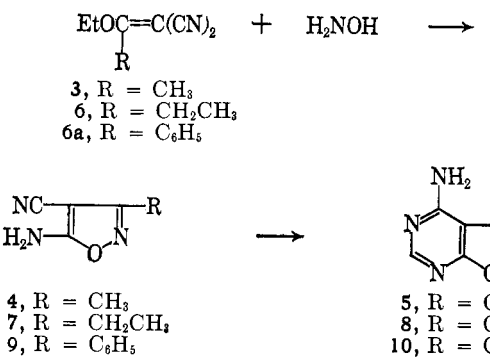
An attractive intermediate for this synthetic sequence would be 5-amino-4-cyanoisoxazole (**2**) which has been described[5] and is readily accessible by the reaction of ethoxymethylenemalononitrile (**1**) with hydroxylamine. However, attempted cyclization of **2** with formamidine acetate[6] in ethanol or 2-ethoxyethanol, a procedure which is successful with other *o*-aminonitriles and leads, in these latter cases, directly



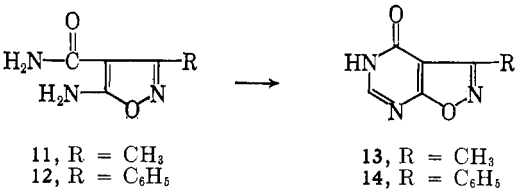
to fused 4-aminopyrimidine heterocycles, was unsuccessful, since **2** proved to be unstable in the presence of alkali. This is not unexpected, for the presence of an unsubstituted 3-position in isoxazole derivatives is known to lead to alkali instability *via* ring cleavage.[7] Evidently replacement of the acidic proton in the 3-position would be a necessary preliminary step if such 5-amino-4-cyanoisoxazole intermediates were to be useful in the synthesis of the desired bicyclic derivatives.

We therefore prepared 5-amino-4-cyano-3-methylisoxazole (**4**) by the reaction of hydroxylamine with methylethoxymethylenemalononitrile (**3**).[8] As expected, compound **4** was stable to alkali, and reaction with formamidine acetate in 2-ethoxyethanol yielded the desired bicyclic compound, 4-amino-3-methylisoxazolo[5,4-*d*]pyrimidine (**5**). The yield in this direct pyrimidine-annulation reaction was disappointingly low, however, and it was found that a two-step sequence involving preliminary treatment of **4** with a mixture of ethyl orthoformate and acetic anhydride, followed by treatment with ethanolic ammonia, led to compound **5** in 77% yield.

Several related 5-amino-4-cyanoisoxazoles then were prepared by the reaction of hydroxylamine with ethylethoxymethylenemalononitrile (**6**) and phenylmethoxymethylenemalononitrile (**6a**)[9] to give the 3-ethyl and 3-phenyl derivatives of 5-amino-4-cyanoisoxazole (**7** and **9**, respectively). Treatment of these aminonitriles with ethyl orthoformate and acetic anhydride followed by ammonia, as described above, led in high yield to the 3-substituted 4-aminoisoxazolopyrimidines **8** and **10**. Compound **9** was a previously known intermediate, having been prepared by Dornow and Teckenburg[10] by an alternative route.



Several 4-hydroxy derivatives of the isoxazolo[5,4-*d*]-pyrimidine system were prepared by conversion of the aminonitriles **4** and **9** by treatment with concentrated sulfuric acid to the carboxamides **11** and **12**, followed by cyclization with a mixture of ethyl orthoformate and acetic anhydride to give 3-methylisoxazolo[5,4-*d*]-pyrimidin-4(5*H*)-one (**13**) and the corresponding 3-phenyl derivative (**14**). The structure of **13** was confirmed by an independent synthesis from **5** by treatment with dilute hydrochloric acid and sodium nitrite.



A similar conversion of compound **10** to **14** was not successful because of the extreme insolubility of **10** in acid solution. Attempts to carry out the conversion of **10** to **14** with nitrosyl sulfuric acid led to extensive decomposition.

We have previously demonstrated[4] with other *o*-aminonitriles that treatment with ethyl orthoformate and acetic anhydride to give the ethoxymethyleneamino derivative, followed by treatment with primary amines, leads *via* the intermediate formation of a formamidine, followed by intramolecular addition to the nitrile group and a subsequent base-catalyzed ring opening–ring closure sequence, to 4-substituted aminopyrimidine heterocycles in good yield. By application of this reaction sequence to the *o*-aminonitriles **4** and **9** and by employing methylamine, 3-dimethylaminopropylamine, and 3-diethylaminopropylamine, the appropriately substituted isoxazolopyrimidines **17**–**22** were readily prepared in good yield.

Since it was conceivable, although not probable, that all of these final products might have been 5-substituted 4-imino rather than the rearranged 4-substituted amino compounds, it was thought desirable to confirm this structural assignment by an independent synthesis of some of these derivatives. By treatment of 4-amino-3-methylisoxazolo[5,4-*d*]pyrimidine (**5**) with a mixture of 3-diethylaminopropylamine and its cor-

(4) For examples and leading references, see E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).

(5) H. Kano, Y. Makisumi, and K. Ogata, *Chem. Pharm. Bull.* (Tokyo), **6**, 105 (1958).

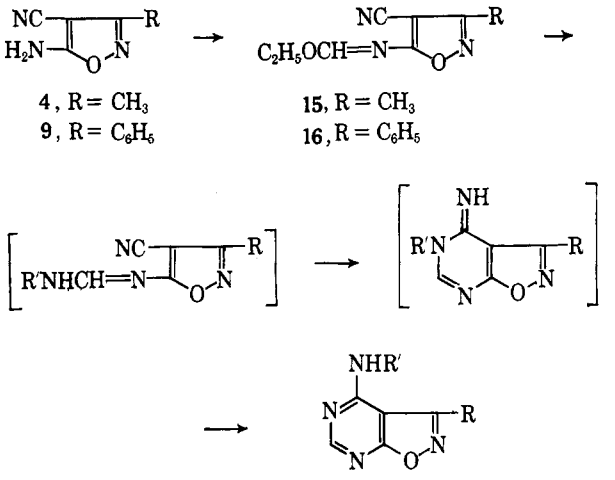
(6) E. C. Taylor and W. A. Ehrhart, *J. Am. Chem. Soc.*, **82**, 3138 (1960).

(7) See (a) R. A. Barnes, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 465; (b) A. Quilico, "The Chemistry of Heterocyclic Compounds. Five- and Six-Membered Compounds with Oxygen and Nitrogen," R. H. Wiley, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, p. 45.

(8) W. Huber and H. A. Hölscher, *Ber.*, **71B**, 99 (1938); Y. Urushibara and M. Takebayashi, *Bull. Chem. Soc. Japan*, **11**, 557 (1936).

(9) A. Dornow and E. Schleese, *Ber.*, **91**, 1830 (1958).

(10) A. Dornow and H. Teckenburg, *ibid.*, **93**, 1103 (1960).



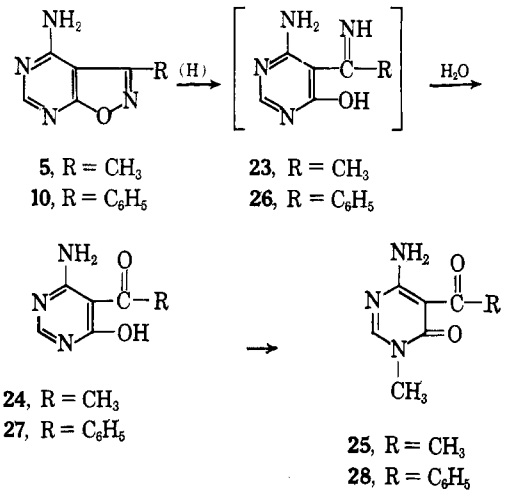
4, R = CH_3
9, R = C_6H_5

15, R = CH_3
16, R = C_6H_5

17, R = CH_3; R′ = CH_3
18, R = CH_3; R′ = $CH_2CH_2CH_2N(CH_3)_2$
19, R = CH_3; R′ = $CH_2CH_2CH_2N(CH_2CH_3)_2$
20, R = C_6H_5, R′ = CH_3
21, R = C_6H_5; R′ = $CH_2CH_2CH_2N(CH_3)_2$
22, R = C_6H_5; R′ = $CH_2CH_2CH_2N(CH_2CH_3)_2$

responding hydrochloride,[11] compound **19** was formed in 24% yield, and it proved to be identical in every respect with the product formed by the ethyl orthoformate–acetic anhydride–amine sequence described above. Similarly, treatment of **10** with 3-diethylaminopropylamine and its hydrochloride gave **22** in 30% yield. Since the ultraviolet spectra of all of the above described 4-substituted amino derivatives in each series (*i.e.*, 3-methyl and 3-phenyl) were essentially identical, we feel confident in assigning the above structures.

It is well known that isoxazole rings are readily cleaved by hydrogenation,[12-15] and it was thought that useful pyrimidine intermediates suitable for further cyclization to condensed pyrimidine heterocycles might be available by reductive cleavage of the isoxazole ring in these bicyclic purine analogs. Thus, catalytic reduction of **5** followed by treatment with water gave 5-acetyl-4-amino-6-hydroxypyrimidine (**24**) in 91% yield. The intermediate imine (**23**), presumably formed as the initial product of the reductive cleavage, proved to be too unstable for characterization. Attempted recrystallization resulted in every case in loss of ammonia, and unsatisfactory analyses were the inevitable result. Attempted capture of the imine **22** by various reagents designed to give a pyrimidopyrimidine were also unpromising because of concomitant hydrolysis. Methylation of **24** with dimethyl sulfate gave **25**, which was readily characterized by the formation of a 2,4-dinitrophenylhydrazone. Similar reductive cleavage of **10** under the same conditions resulted in the rapid uptake of 1 mole of hydrogen, and treatment of the reduction mixture with water then gave 4-amino-5-benzoyl-6-hydroxypyrimidine (**27**), which was also characterized as its monomethyl derivative **28**. The position of methylation in **24** and **27** is assumed to be on N-1 as shown by analogy with the known methylation of 4-amino-6-hydroxypyrimidine to 4-amino-1-methylpyrimidin-6(1*H*)-one and by the observation that both methyl derivatives (**25** and **28**) are stable to alkali.[16]



5, R = CH_3
10, R = C_6H_5

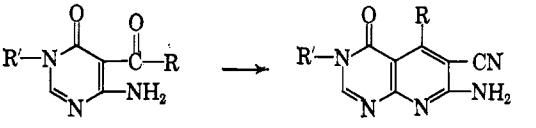
23, R = CH_3
26, R = C_6H_5

24, R = CH_3
27, R = C_6H_5

25, R = CH_3
28, R = C_6H_5

The unreactivity of the ketone grouping in **27** is worthy of note. It proved to be extremely difficult to characterize **27** in the form of its carbonyl derivatives, for the benzoyl grouping was unreactive towards such reagents as phenylhydrazine and hydroxylamine (although it slowly formed a 2,4-dinitrophenylhydrazone). The decreased carbonyl reactivity of **27** compared with **24** is probably due to the increase in steric hindrance in the former compound. It should be noted that 5-acyl derivatives of 4,6-disubstituted pyrimidines are notably unreactive towards carbonyl reagents.[17]

Several experiments were carried out which serve to illustrate the potential usefulness of these 5-aroyl and 5-acyl 6-aminopyrimidines as intermediates for the preparation of condensed pyrimidine heterocycles. For example, the reaction of **24** with malononitrile in pyridine led in 54% yield to the pyridopyrimidine **29**. Similarly, **28** reacted with malononitrile in pyridine to give the pyridopyrimidine **30** in 22% yield. Presumably the lower yield in the latter case was also the result of steric hindrance at the carbonyl group. However, less reactive methylene derivatives, such as phenylacetonitrile, ethyl cyanoacetate, and cyanoacetamide, failed to react.



24, R = CH_3; R′ = H
28, R = C_6H_5; R′ = CH_3

29, R = CH_3; R′ = H
30, R = C_6H_5; R′ = CH_3

Experimental[18]

5-Amino-4-cyano-3-methylisoxazole (**4**).—To 14 g. (0.2 mole) of hydroxylamine hydrochloride dissolved in 80 ml. of 10% sodium hydroxide was added, with vigorous stirring, 27.2 g. (0.2 mole) of methylethoxymethylenemalononitrile (prepared according to the method of Huber and Hölscher[8]). The tempera-

(11) For examples of acid-catalyzed amidine exchange reactions of this type, see C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **82**, 3973 (1960).
(12) G. Shaw, *J. Chem. Soc.*, 720 (1950).
(13) G. Stagno D'Alcontres, *Gazz. chim. ital.*, **80**, 441 (1950).
(14) L. Panizzi, *ibid.*, **76**, 44 (1946).
(15) G. N. Walker, *J. Org. Chem.*, **27**, 1929 (1962).
(16) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1298 (1961).
(17) W. Pfleiderer and G. Strauss, *Ann.*, **612**, 178 (1958).
(18) All melting points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. All ultraviolet spectra were determined in ethanol.

ture was kept below 50° by making this addition slowly and by addition of small amounts of ice. After stirring for an additional 1.5 hr. at approximately 20°, the colorless solid was filtered, washed with water, and recrystallized from aqueous ethanol to give white needles, m.p. 222–224° dec., yield 17.2 g. (71%).

Anal. Calcd. for $C_5H_5N_3O$: C, 48.78; H, 4.10; N, 34.14. Found: C, 48.59; H, 4.17; N, 34.18.

Ethylethoxymethylenemalononitrile (6).—A solution of 15 g. (0.22 mole) of malononitrile in a mixture of 47.5 g. (0.27 mole) of triethyl orthopropionate and 75 ml. of acetic anhydride was refluxed for 9.5 hr. After removal of the excess reagents *in vacuo*, distillation gave 27.3 g. (82%) of yellow liquid, b.p. 118–120° (2.7 mm.).[19] This substance was used immediately after its preparation.

5-Amino-4-cyano-3-ethylisoxazole (7).—This compound was prepared from ethylethoxymethylenemalononitrile in the same manner as compound **4**. The crude product was recrystallized from ethanol–petroleum ether (b.p. 60–70°) to give white crystals, m.p. 139–140°, 82% yield.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.54; H, 5.15; N, 30.64. Found: C, 52.49; H, 5.01; N, 30.74.

5-Amino-4-cyano-3-phenylisoxazole (9) was prepared according to the directions of Dornow and Teckenburg.[10] The phenylmethoxymethylenemalononitrile required in this preparation was generously donated by Smith Kline and French Laboratories, Philadelphia, Pa.

4-Cyano-5-ethoxymethyleneamino-3-methylisoxazole (15).—A solution of 10 g. (0.081 mole) of 5-amino-4-cyano-3-methylisoxazole (**4**) in 25 ml. of acetic anhydride and 37 ml. of triethyl orthoformate was refluxed for 4 hr. while protected against moisture with a calcium chloride tube. Concentration *in vacuo* (0.1 mm.) gave a brown oil which crystallized upon immersion in ice. Recrystallization from petroleum ether (b.p. 60–70°) gave 12.3 g. (84%) of white needles, m.p. 33–34°. A small amount of higher melting solid insoluble in petroleum ether was removed by filtration and discarded.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.42; H, 5.50; N, 23.20.

4-Amino-3-methylisoxazolo[5,4-*d*]pyrimidine (5). **A.**—A solution of 10 g. (0.081 mole) of 5-amino-4-cyano-3-methylisoxazole (**4**) in an equimolar mixture of 25 ml. of acetic anhydride and 37 ml. of triethyl orthoformate was refluxed for 4 hr. After concentration *in vacuo* the residual oil was poured into 100 ml. of ethanolic ammonia. Precipitation occurred immediately. After 2 hr. of stirring at room temperature the mixture was refrigerated. Filtration, washing with water, and vacuum drying gave 8.9 g. of white solid, m.p. 303–305° dec. An additional 0.6 g. of product separated from the filtrate upon standing; yield 9.5 g. (77%). Recrystallization from aqueous ethanol (large volume) or dimethylformamide–ethanol gave colorless crystals, m.p. 303–305° dec.; λ_{max} 249, 273 mμ ($\epsilon \times 10^3$ 7.7, 5.7).

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.77; H, 4.00; N, 37.05.

B.—The addition of 10 g. (0.056 mole) of recrystallized 4-cyano-5-ethoxymethyleneamino-3-methylisoxazole to approximately 100 ml. of ethanolic ammonia, followed by stirring at room temperature for 1 hr., gave 7.0 g. (83%) of white crystals, m.p. 300–302° dec., identical with the product prepared by method A.

4-Amino-3-ethylisoxazolo[5,4-*d*]pyrimidine (8) was prepared in the same manner as described above for compound **5** except that 10 g. of 5-amino-4-cyano-3-ethylisoxazole (**7**) was employed. The yield was 9.0 g. (75%) of white solid, m.p. 219–221°. Recrystallization from a large volume of ethanol yielded small, white needles, m.p. 221–222°; λ_{max} 249, 272 mμ ($\epsilon \times 10^3$ 10.6, 7.8).

Anal. Calcd. for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.22; H, 4.90; N, 34.16.

4-Cyano-5-ethoxymethyleneamino-3-phenylisoxazole (16).—A solution of 10 g. (0.054 mole) of 5-amino-4-cyano-3-phenylisoxazole (**9**) in 25 ml. of acetic anhydride and 37 ml. of triethyl orthoformate was refluxed for 4 hr. Upon cooling to room temperature, long white needles separated. Filtration and concentration of the filtrate gave 12 g. (92%) of product, m.p. 110–112°, which upon recrystallization from ethanol melted at 111–112°.

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60. Found: C, 64.45; H, 4.71.

4-Amino-3-phenylisoxazolo[5,4-*d*]pyrimidine (10).—Anhydrous ammonia was bubbled through a stirred suspension of 10 g. (0.042 mole) of 4-cyano-5-ethoxymethyleneamino-3-phenylisoxazole (**16**) in 150 ml. of ethanol at room temperature for 2 hr. Initially a viscous yellow-green mixture formed, but, as more ammonia was added, the alcohol became warm and a more fluid suspension resulted. After cooling, filtration, and concentration of the filtrate to a small volume, 7.5 g. (84%) of white solid was obtained. Recrystallization from aqueous ethanol yielded shiny white plates, m.p. 211–212°; λ_{max} 244, 276 mμ ($\epsilon \times 10^3$ 12.4, 8.2).

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.26; H, 3.77; N, 26.41. Found: C, 62.34; H, 3.96; N, 26.36.

5-Amino-3-methylisoxazole-4-carboxamide (11).—To 35 ml. of concentrated sulfuric acid was added slowly with stirring 5.0 g. (0.04 mole) of 5-amino-4-cyano-3-methylisoxazole (**4**). The temperature reached 55° during the addition. The solution, still stirred, was heated at 50–55° for 1 hr. and then left at room temperature for an additional hour. Cautious addition to crushed ice yielded a white solid which slowly dissolved as the stirred mixture was allowed to warm to room temperature. Concentrated ammonium hydroxide was carefully added, with ice cooling, to pH 9 and the resulting suspension was refrigerated overnight to give 3.8 g. (68%) of a crystalline white solid. Recrystallization from ethanol–petroleum ether gave small, white crystalline rods, m.p. 190–193° dec.

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.79; H, 4.54; N, 29.80.

5-Amino-3-phenylisoxazole-4-carboxamide (12.)—Using a similar procedure, 5.0 g. (0.027 mole) of 5-amino-4-cyano-3-phenylisoxazole (**9**) gave 4.6 g. (83%) of product (the addition of ammonium hydroxide in this reaction was made directly to the suspension 1 hr. after the mixture was poured onto ice). Recrystallization from water yielded white needles, m.p. 178–180°.

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46. Found: C, 59.19; H, 4.39.

3-Methylisoxazolo[5,4-*d*]pyrimidin-4(5*H*)-one (13.)—A solution of 2.0 g. (0.014 mole) of 5-amino-3-methylisoxazole-4-carboxamide (**11**) in 15 ml. of acetic anhydride and 15 ml. of triethyl orthoformate was refluxed for 3 hr. The resulting orange solution was concentrated to dryness *in vacuo*, and the residue was dissolved in ammonium hydroxide (Norit), filtered, and acidified with acetic acid. After refrigeration for 2 hr., filtration, and vacuum drying, 1.4 g. of product, m.p. 214–218° dec., was obtained. Recrystallization from ethanol gave white needles, m.p. 219–221° dec. For analysis a sample was recrystallized from ethanol–petroleum ether (b.p. 60–70°); λ_{max} 235, 242 (sh), 267 mμ ($\epsilon \times 10^3$ 6.4, 6.0, 5.4).

Anal. Calcd. for $C_6H_5N_3O_2$: C, 47.68; H, 3.34; N, 27.81. Found: C, 47.65; H, 3.55; N, 27.56.

Diazotization of 4-amino-3-methylisoxazolo[5,4-*d*]pyrimidine (**5**) with sodium nitrite in dilute hydrochloric acid at 0°, followed by stirring at room temperature overnight, gave a product, m.p. 218–219° dec., which was identical in every respect (mixture melting point and infrared spectrum) with that obtained by cyclization of the amide.

3-Phenylisoxazolo[5,4-*d*]pyrimidin-4(5*H*)-one (14) was prepared in 75% yield from 5-amino-3-phenylisoxazole-4-carboxamide (**12**) by a procedure analogous to that described above for the preparation of **13**. The crude product, m.p. 237–239° dec., was recrystallized from ethanol–petroleum ether (b.p. 60–70°) to give colorless platelets, m.p. 239–241° dec.; λ_{max} 249 mμ ($\epsilon \times 10^3$ 15.7).

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 62.29; H, 3.32; N, 19.85.

3-Methyl-4-methylaminoisoxazolo[5,4-*d*]pyrimidine (17).—Anhydrous methylamine was bubbled through a solution of 2.0 g. (0.011 mole) of 4-cyano-5-ethoxymethyleneamino-3-methylisoxazole (**15**) in 30 ml. of ethanol for approximately 1.5 hr., with gentle heating. Solid separated from the reaction mixture after 0.5 hr. Cooling and filtering gave 1.4 g. of a white crystalline solid; the filtrate upon standing gave an additional 0.1 g. of product; the total yield was 1.5 g. (83%). Recrystallization from 1-butanol yielded clusters of white crystals, m.p. 237–238°; λ_{max} 252, 283 mμ ($\epsilon \times 10^3$ 9.8, 9.1).

Anal. Calcd. for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.37; H, 4.86; N, 34.18.

3-Methyl-4-(3′-dimethylaminopropylamino)isoxazolo[5,4-*d*]-pyrimidine (18).—A solution of 5.4 g. (0.03 mole) of 4-cyano-5-

(19) This compound previously has been reported [C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **78**, 5296 (1956)] to have b.p. 142° (7 mm.).

ethoxymethyleneamino-3-methylisoxazole (**15**) and 3.2 g. (slight molar excess) of 3-dimethylaminopropylamine in 50 ml. of ethanol was refluxed for 3 hr. Upon cooling to room temperature, a white crystalline solid precipitated. Filtration and vacuum drying yielded 5.5 g. (78%) of product, m.p. 165–168°. Concentration of the filtrate gave 0.8 g. of uncyclized solid. Recrystallization of the cyclized product from ethanol gave white needles, m.p. 168–169°; λ_{max} 253, 284 mμ ($\epsilon \times 10^3$ 10.3, 9.5).

Anal. Calcd. for $C_{11}H_{17}N_3O$: C, 56.15; H, 7.28; N, 29.77. Found: C, 56.45; H, 7.41; N, 29.40.

3-Methyl-4-(3′-diethylaminopropylamino)isoxazolo[5,4-*d*]pyrimidine (19). A.—An ethanolic solution (20 ml.) containing 1.8 g. (0.01 mole) of 4-cyano-5-ethoxymethyleneamino-3-methylisoxazole (**15**) and 1.3 g. (0.01 mole) of 3-diethylaminopropylamine was refluxed for 3 hr. The ethanol was removed *in vacuo*, and the residue was suspended in *n*-heptane and filtered, yielding 2.3 g. (88%). Recrystallization from *n*-heptane gave white plates, m.p. 93–94°; λ_{max} 253, 284 mμ ($\epsilon \times 10^3$ 10.8, 10.1).

Anal. Calcd. for $C_{13}H_{21}N_5O$: C, 59.29; H, 8.04; N, 26.60. Found: C, 59.34; H, 7.97; N, 26.50.

B.—A mixture of 1.5 g. (0.01 mole) of 4-amino-3-methylisoxazolo[5,4-*d*]pyrimidine (**5**), 5 ml. of 3-diethylaminopropylamine, and 2.0 g. of its hydrochloride was heated for 3 hr. at 145–155°. Repeated extraction of the resulting dark viscous oil with hot *n*-heptane followed by removal of the solvent under reduced pressure gave 0.65 g. (24%) of a yellow solid. Recrystallization from *n*-heptane yielded white crystals, m.p. 91–93°, identical in every respect (infrared and mixture melting point) with the product obtained by method A.

4-Methylamino-3-phenylisoxazolo[5,4-*d*]pyrimidine (20).—To a saturated solution of anhydrous methylamine in 40 ml. of ethanol was added 2.0 g. (0.008 mole) of 4-cyano-5-ethoxymethyleneamino-3-phenylisoxazole (**16**). After stirring for 4 hr. at room temperature, the mixture was refrigerated. Filtration and concentration of the filtrate to a small volume gave 0.9 g. (50%) of white crystals which were recrystallized from dimethylformamide–ethanol to give large white crystalline plates, m.p. 222–224°; λ_{max} 240, 290 mμ ($\epsilon \times 10^3$ 11.0, 8.1).

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.62; H, 4.43; N, 24.88.

3-Phenyl-4-(3′-dimethylaminopropylamino)isoxazolo[5,4-*d*]pyrimidine (21).—A solution of 2.8 g. (0.12 mole) of 4-cyano-5-ethoxymethyleneamino-3-phenylisoxazole (**16**) and 1.1 g. (slight molar excess) of 3-dimethylaminopropylamine in 80 ml. of ethanol was refluxed for 4 hr. and filtered to remove a small amount of undissolved solid; the filtrate was evaporated to dryness under reduced pressure. The residual oil which solidified upon being swirled with a little *n*-heptane was filtered to yield 2.6 g. (74%) of product. Evaporation of the filtrate to dryness gave uncyclized material as shown by the presence of nitrile absorption in the infrared. Recrystallization of the product from *n*-heptane yielded white needles, m.p. 79–80°; λ_{max} 238, 291 mμ ($\epsilon \times 10^3$ 12.4, 8.9).

Anal. Calcd. for $C_{16}H_{19}N_5O$: C, 64.62; H, 6.44; N, 23.55. Found: C, 64.69; H, 6.46; N, 23.26.

3-Phenyl-4-(3′-diethylaminopropylamino)isoxazolo[5,4-*d*]pyrimidine (22). A.—A mixture of 2.1 g. (0.01 mole) of 4-amino-3-phenylisoxazolo[5,4-*d*]pyrimidine (**10**), 5 ml. of 3-diethylaminopropylamine, and 2.0 g. of its hydrochloride was heated for 3 hr. at 140–145°. The dark brown oil was covered with 15 ml. of water and the flask was shaken vigorously. Filtration give a sticky, pale green solid. Recrystallization from *n*-heptane (Norit) yielded 1.0 g. (30%) of white crystals, m.p. 85–87°; λ_{max} 238, 291 mμ ($\epsilon \times 10^3$ 12.0, 9.1).

Anal. Calcd. for $C_{18}H_{23}N_5O$: C, 66.44; H, 7.12; N, 21.52. Found: C, 66.46; H, 7.05; N, 21.61.

B.—A solution of 2.4 g. (0.01 mole) of 4-cyano-5-ethoxymethyleneamino-3-phenylisoxazole (**16**) in 70 ml. of hot ethanol was treated with 1.3 g. (0.01 mole) of 3-diethylaminopropylamine and refluxed for 3 hr. After cooling to room temperature, filtration removed a trace amount of undissolved solid. Removal of the solvent under reduced pressure gave an oil which crystallized to 2.6 g. (80%) of a white solid, m.p. 81–84° upon trituration with *n*-heptane. This was identical in every respect with the product obtained by method A.

5-Acetyl-4-amino-6-hydroxypyrimidine (24).—A solution of 3.0 g. (0.02 mole) of 4-amino-3-methylisoxazolo[5,4-*d*]pyrimidine (**5**) in 180 ml. of dimethylformamide was hydrogenated with 0.4 g. of 10% palladium on charcoal, with magnetic stirring, at room temperature (22°) and atmospheric pressure. Reduction ceased after 1 mole of hydrogen was absorbed. After removing the catalyst by filtration, the clear filtrate was distilled to dryness at 22° (1 mm.). The residual white solid was covered with 100 ml. of water, boiled for 30 min. with magnetic stirring (ammonia evolved), and then dissolved by the addition of 10% sodium hydroxide. After standing at room temperature for 1.5 hr., acidification with glacial acetic acid gave 2.8 g. (91%) of white solid, m.p. 308–310° dec. This substance gave a positive haloform test. Recrystallization from water yielded small clusters of white needles, m.p. 310–311° dec.

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.05; H, 4.61. Found: C, 47.21; H, 4.40.

5-Acetyl-4-amino-1-methylpyrimidin-6(1*H*)-one (25).—A solution of 2.0 g. (0.013 mole) of 5-acetyl-4-amino-6-hydroxypyrimidine (**24**) in 15 ml. of *ca.* 7% sodium hydroxide was treated with 3 ml. of dimethyl sulfate and stirred for 1.5 hr. at room temperature. Filtration gave 1.4 g. (63%) of a white solid, m.p. 210–215°. Recrystallization from ethanol yielded white needles, m.p. 214–215°; infrared, $\lambda_{max}^{CHCl_3}$ 5.98 μ (–C(=O)–CH$_3$).

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43. Found: C, 50.51; H, 5.41.

A 2,4-dinitrophenylydhrazone was prepared in methanol.

Anal. Calcd. for $C_{13}H_{13}N_7O_5$: N, 28.27. Found: N, 28.58.

4-Amino-5-benzoyl-6-hydroxypyrimidine (27) was prepared in 72% yield from 4-amino-3-phenylisoxazolo[5,4-*d*]pyrimidine (**10**) in the manner described above for the preparation of **24** from **5**. Recrystallization of the crude product, m.p. 290–292° dec., from dimethylformamide–ethanol gave small, white glistening crystals, m.p. 292–294° dec.

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22. Found: C, 61.42; H, 4.18.

4-Amino-5-benzoyl-1-methylpyrimidin-6(1*H*)-one (28).—A solution of 3.0 g. (0.014 mole) of 4-amino-5-benzoyl-6-hydroxypyrimidine (**27**) in 17 ml. of 10% sodium hydroxide was treated with 5 ml. of dimethyl sulfate and stirred for 1.25 hr. at room temperature. The resulting white solid was filtered, washed with a little water, and dried *in vacuo*, yielding 2.8 g. (89%). Recrystallization from ethanol gave shiny white platelets, m.p. 225–227°; infrared, $\lambda_{max}^{CHCl_3}$ 5.99 μ (–C(=O)–C$_6$H$_5$).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.57; H, 5.03; N, 18.20.

7-Amino-6-cyano-5-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (29).—A solution of 1.0 g. (0.0065 mole) of 5-acetyl-4-amino-6-hydroxypyrimidine (**24**) and 0.5 g. (0.007 mole) of malononitrile in 70 ml. of pyridine was heated under reflux with stirring. Solid started to separate from the reaction mixture after 0.5 hr. After 18 hr. of refluxing, the mixture was filtered hot to give 0.7 g. (54%) of a yellow solid, m.p. >340°. Unchanged starting material was recovered by cooling of the filtrate. The product was prepared for analysis by vacuum sublimation (290° at 0.25 mm.); infrared, λ_{max}^{Nujol} 4.51 μ (–CN).

Anal. Calcd. for $C_9H_7N_5O$: C, 53.73; H, 3.51; N, 34.81. Found: C, 53.68; H, 3.46; N, 34.92.

7-Amino-6-cyano-3-methyl-5-phenylpyrido[2,3-*d*]pyrimidin-4(3H)-one (30).—A solution of 0.9 g. (0.004 mole) of 4-amino-5-benzoyl-1-methylpyrimidin-6(1*H*)-one (**28**) and 0.35 g. (0.005 mole) of malononitrile in 15 ml. of pyridine was heated under reflux for 18 hr. The solvent was removed by evaporation under reduced pressure and the residue was triturated with water and filtered. Extraction of the solid with chloroform and filtration gave 0.25 g. (22%) of yellow product, m.p. >340°, which was recrystallized from dimethylformamide for analysis; infrared, λ_{max}^{Nujol} 4.53 μ (–CN).

Anal. Calcd. for $C_{15}H_{11}N_5O$: C, 64.97; H, 4.00. Found: C, 64.68; H, 4.06.