with I was carried out in glacial acetic acid. However, only the pyrimidine was obtained.

EXPERIMENTAL[19]

General. The essential features of several examples of the pyrimidine-forming reaction are summarized in Table I. The products often crystallized directly from the reaction mixture in good purity but could be recrystallized readily from water or alcohol. Detailed illustrations are given below.

4-Amino-5-carbethoxypyrimidine. A mixture of 12.2 g. (0.15 mole) of I and 25.1 g. (0.15 mole) of 2-carbethoxyacetamidine hydrochloride[20] in 45 cc. of acetonitrile reacted moderately exothermically when heated to about 75°. It was subsequently heated at reflux for 1.5 hr. The superior solution was then decanted hot from the partly crystallized insoluble formamidine hydrochloride and the residue was re-extracted with fresh boiling acetonitrile. The combined solutions gave on cooling 21.7 g. of the pyrimidine, m.p. 101–102°. (Yield, 85%.) After recrystallization from acetonitrile or benzene the product melted at 102–104°.

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43. Found: C, 50.11; H, 5.53.

Hydrolysis in hot 2*N* sodium hydroxide gave 4-amino-5-carboxypyrimidine, m.p. 274–275°; lit.[10a] m.p. 278–281°.

5-Carbethoxy-4-ethoxypyrimidine. Ethyl 2-carbethoxyacetimidate hydrochloride[21] (7.8 g., 0.040 mole) was shaken with 3.25 g. (0.040 mole) of I in 10 cc. of ethanol until the mildly exothermic reaction subsided. After an additional hour at room temperature, the mixture was filtered to remove 0.75 g. of ammonium chloride. Evaporation of the ethanol and crystallization of the residue from acetonitrile gave 2.5 g. of formamidine hydrochloride, m.p. *ca.* 80°. (75%.) The mother liquor was then distilled yielding 4.0 g. (51%) of the pyrimidine, b.p. 87–92° at 0.2 mm. The product was redistilled for analysis (b.p. 82–85° at 0.1 mm.).

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.18; H, 6.34; N, 14.39.

Hydrolysis of a small sample with 6*N* hydrochloric acid gave *4-hydroxypyrimidine-5-carboxylic acid,* m.p. 228.5–230.5° dec., identical with material previously[4] obtained by hydrolysis of 5-carbethoxy-4-hydroxypyrimidine.

5-Benzoyl-4-ethoxypyrimidine. A mixture of 8.1 g. (0.10 mole) of I and 22.8 g. (0.10 mole) of ethyl benzoylacetimidate hydrochloride[22] was shaken in 20 cc. of ethanol. As the mildly exothermic reaction proceeded a clear solution was obtained which solidified to a yellow cake when cooled. This was broken up and filtered, yielding 22.8 g., m.p. *ca.* 46°; crude yield, 100%. Recrystallization of the crude product from ethanol gave colorless needles, m.p. 67–69°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 67.96; H, 5.42; N, 12.56.

The identity of this product was further established by hydrolytic degradation. Hydrolysis of 2.5 g. in boiling 10% hydrochloric acid followed by neutralization with sodium carbonate gave 1.3 g. of *5-benzoyl-4-hydroxypyrimidine.* After recrystallization from water this melted at 185–187°.

Anal. Calcd. for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 66.15; H, 4.27; N, 14.10.

Methyl 2-cyanothioacetimidate hydrochloride was prepared by passing methyl mercaptan into a cold solution of equimolar amounts of malononitrile and hydrogen chloride in ether. The product crystallized during the addition and during the following 24-hour storage under refrigeration. The yield was 65%, m.p. 134–137° dec. This compound appeared to be unstable in storage and was used shortly after preparation. Volhard analysis for chloride gave somewhat high results.

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(19) Melting points were determined by the capillary method and are uncorrected. Microanalyses were carried out in these laboratories under the direction of Dr. J. A. Kuck or by the Galbraith Microanalytical Laboratories. Infrared spectra were interpreted by Mr. N. B. Colthup and Dr. J. E. Lancaster.

(20) S. M. McElvain and B. E. Tate, *J. Am. Chem. Soc.*, **73**, 2760 (1951).

(21) A. Pinner, *Ber.*, **28**, 473 (1895).

(22) A. Haller, *Bull. soc. chim.*, [2] **48**, 24 (1887).

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT, CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID COMPANY]

Reaction of s-Triazine with Acidic α-Methylene Compounds[1]

K. ROBERT HUFFMAN, FRED C. SCHAEFER, AND GRACE A. PETERS

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The condensation of *s*-triazine with a variety of active methylene compounds has been studied. In addition to 4,5-disubstituted pyrimidines, the products of these reactions include pyridines, aminomethylene derivatives, glutaconitrile derivatives, and substituted formamidines, depending upon the nature of the starting material and the experimental conditions. The mechanism of formation of the various products is discussed.

The reaction of *s*-triazine (I) with imidates, amidines, and amidine salts has been shown to be a synthetically useful method for the preparation of monosubstituted *s*-triazines in general[2,3] and also of 4,5-disubstituted pyrimidines in the particular case in which the imidate or amidine contains an acidic α-methylene group.[1] Consideration of the probable mechanism of pyrimidine formation, in which the initial step was assumed to be attack of the methylene group upon an electron deficient carbon atom in the triazine ring,[1] suggested that the amidine or imidate moiety was perhaps not a necessary feature and that other active methylene compounds might react similarly with I.

(1) Pyrimidine Synthesis, Part II. For Paper I, see F. C. Schaefer, K. R. Huffman, and G. A. Peters, *J. Org. Chem.*, **27**, 548 (1962).

(2) F. C. Schaefer and G. A. Peters, *J. Am. Chem. Soc.*, **81**, 1470 (1959).

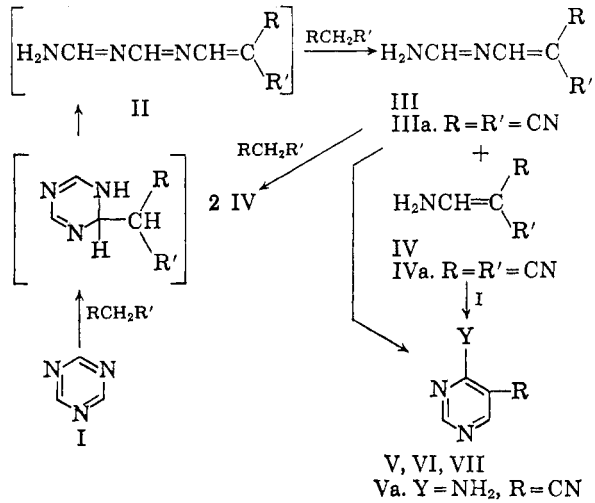
(3) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2784 (1961).

A recent study by Kreutzberger and Grundmann[4] has in fact demonstrated that such reactions do occur; these authors obtained pyrimidines from the reactions of I with diethyl malonate and ethyl benzoylacetate at elevated temperatures. Examples of the formation of aminomethylene derivatives from I and active methylene compounds were also reported.

In a continuation of our study of the utility of *s*-triazine as a synthetic intermediate, we have independently investigated several of these same reactions, usually under different reaction conditions, and, in some cases, have obtained different results. In addition, the use of a wider variety of active methylene reagents, together with the use of bases to promote reactivity, has afforded a wider variety of products. This in turn has provided more information concerning the mechanism of these reactions, thus leading to an interpretation somewhat different from that of Kreutzberger and Grundmann.

Perhaps the most interesting and mechanistically informative reaction studied in this series was that between I and malononitrile. When these reagents were mixed in ethanol, in the absence of added base, an exothermic reaction occurred and a bright yellow high melting solid rapidly crystallized in yields[5] up to 37%. Contrary to the literature report[4] this was not the expected pyrimidine Va; it was assigned the structure *N*-(2,2-dicyanovinyl)formamidine (IIIa) on the basis of analysis, spectral properties, and further reactions.[6] From the filtrate 3-amino-2-cyanoacrylonitrile (IVa) was obtained as the major product.[7] Compound IIIa was readily converted in high yield to the isomeric 4-amino-5-cyanopyrimidine (Va) by heating with a catalytic amount of base or by boiling with water.[8] It reacted rapidly upon further treatment with malononitrile in dimethylformamide at 25° to give IVa in 86% yield. The latter reaction was extremely slow in ethanol because of the insolubility of IIIa in this medium. When I and malononitrile were mixed in dimethylformamide, crystallization of IIIa was avoided and IVa was isolated in 91% yield.

Chart I



Further experiments revealed that the aminomethylene derivative IVa reacted with *s*-triazine in the presence of sodium ethoxide in refluxing ethanol to give a good yield of the pyrimidine Va. Finally, it was found that, in the presence of added base in refluxing ethanol, malononitrile and I afforded Va in yields of up to 80%. The above results strongly indicated that both IIIa and IVa were intermediates in the base-catalyzed conversion of I to the pyrimidine Va. This was confirmed by subsequent experiments in which both IIIa and IVa were isolated from the early stages of a base catalyzed reaction.

The probable course of the reaction of I with malononitrile is shown in Chart I. The identification and characterization of IIIa as one of the primary products is the key point in support of this reaction pathway over the one proposed by Kreutzberger and Grundmann.[4] The latter workers proposed that the primary process involved the addition of three equivalents of the active methylene reagent to I, forming a hexahydrotriazine derivative which then broke down to give three equivalents of the aminomethylene derivative IV. Compound IV was viewed as reacting further with *s*-triazine giving an intermediate of type III which finally cyclized to the pyrimidine. For the case of the uncatalyzed reaction with malononitrile, at

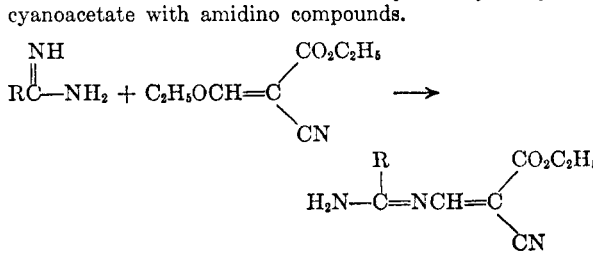
(4) A. Kreutzberger and C. Grundmann, *J. Org. Chem.*, 26, 1121 (1961).

(5) All yields quoted are based on the active methylene reagent, unless otherwise specified, as an excess over the stoichiometric amount of I was used in most reactions.

(6) Since the experimental conditions were the same this is undoubtedly the same "yellow substance" as was obtained by Kreutzberger and Grundmann,[4] who inadvertently converted it to Va in the course of attempted purification.

(7) By varying the relative amounts of starting materials in this reaction it was determined that the *s*-triazine is completely utilized. Thus, in the presence of excess malononitrile the combined yield of IIIa and IVa was quantitative when calculated per HCN unit of I. This requires that at least one of the two products must be formed in a secondary reaction of malononitrile with a fragment of the triazine ring or an intermediate containing all of the elements of the *s*-triazine molecule.

(8) Similar intermediates in pyrimidine synthesis have been isolated from the reaction of ethyl ethoxymethylenecyanoacetate with amidino compounds.



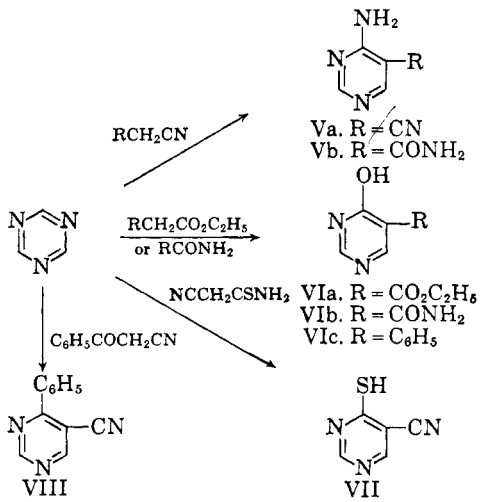
See T. B. Johnson, *Am. Chem. J.*, 42, 505 (1909); A. R. Todd and F. Bergel, *J. Chem. Soc.*, 364 (1937); A. Dornow and G. Petsch, *Ann.*, 588, 45 (1954).

least, the mechanism of Kreutzberger and Grundmann is untenable, as the aminomethylene compound IVa does not react with I under the mild conditions employed.

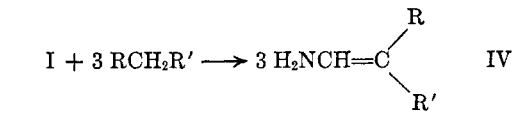
Extension of our investigation to other active methylene compounds showed that a variety of such reagents could be converted to 4,5-disubstituted pyrimidines by condensation with *s*-triazine in refluxing ethanol containing sodium ethoxide. Cyclization occurred readily in many, but not all, cases with such groups as nitrile, ester, amide, and thioamide to give pyrimidines containing amino, hydroxy, and mercapto groups in the 4-position as depicted in Chart II. Thus the utility of the synthetic method was demonstrated.[9]

Pyrimidine formation with benzoylacetonitrile unexpectedly proceeded with cyclization at the benzoyl group to give 5-cyano-4-phenylpyrimidine (VIII), rather than the 4-amino-5-benzoyl derivative. The reaction of I with ethyl benzoylacetate was reported[4] to give 5-carbethoxy-4-phenylpyrimidine in similar fashion. This is apparently not a general type of reaction, however, as acetylacetone and ethyl acetoacetate did not give pyrimidines when condensed with I, and other ketones such as dibenzoylmethane and 5,5-dimethyl-1,3-cyclohexanedione were recovered unchanged from treatment with I under the usual conditions for pyrimidine formation.

CHART II



Aminomethylene derivatives (IV) were sometimes obtained in good yields from active methylene compounds which did not give heterocyclic products by the above procedure. Moreover, as with malononitrile, the reaction of I with cyanoacetamide could be controlled by proper choice of conditions to give either pyrimidine Vb or aminomethylene compound IVb. Optimum conditions for preparation of compounds of type IV varied widely among various active methylene reagents. Although yields of crude products were sometimes excellent, the method provides no particular advantage over other reported preparations which employ more common reagents.[10-12] Consequently, isolation of IV was not attempted in every case.



IVa. R = R' = CN
IVb. R = CN; R' = $CONH_2$
IVc. R = CN; R' = $CO_2C_2H_5$
IVd. R = R' = $COCH_3$

Although intermediates of type III were not isolated in any cases other than IIIa, it is nevertheless reasonable to assume that the reaction sequence shown in Chart I is general for these reactions of *s*-triazine. The isolation of IIIa is considered to be the result of a fortunate coincidence of mild reaction conditions possible with malononitrile and low solubility of the product IIIa, a situation which was not duplicated with other reagents.

As the base-promoted reaction of *s*-triazine with active methylene compounds to give pyrimidines usually proceeded smoothly, it was surprising that, in some instances, apparently analogous compounds failed to react in the same manner. Thus, while malononitrile and cyanoacetamide readily condensed with I to give the pyrimidines Va and Vb, respectively, reaction of I with ethyl cyanoacetate under similar conditions gave no pyrimidine. In the presence of one equivalent of sodium ethoxide, I and ethyl cyanoacetate led to the known sodium salt of diethyl 2,2'-dicyanoglutaconate (Xc) as the major product, while a catalytic amount of the same base produced IVc in 98% yield. In the absence of added base, a mixture of IVc and the formamidine salt of diethyl 2,2'-dicyanoglutaconate (IXc) was obtained.[13] The structure of IXc was proved by conversion to Xc upon treatment with aqueous sodium chloride and by isolation of formamidine picrate upon reaction of IXc with picric acid. Benzoylacetonitrile reacted with I in a somewhat similar manner. In the absence of added base a corresponding mixture of IVe and IXe was formed, although the base-catalyzed reaction did yield the aforementioned 5-cyano-4-phenylpyrimidine (VIII).

The probable route by which the glutacononitrile derivatives are formed is shown in Chart III. The reaction of I with ethyl cyanoacetate, for example, may proceed to give IIIc and IVc in the usual manner. The intermediate IIIc can appar-

(9) The disadvantages of previous methods for synthesis of 2-unsubstituted pyrimidines have been pointed out in ref. 1 and 4.

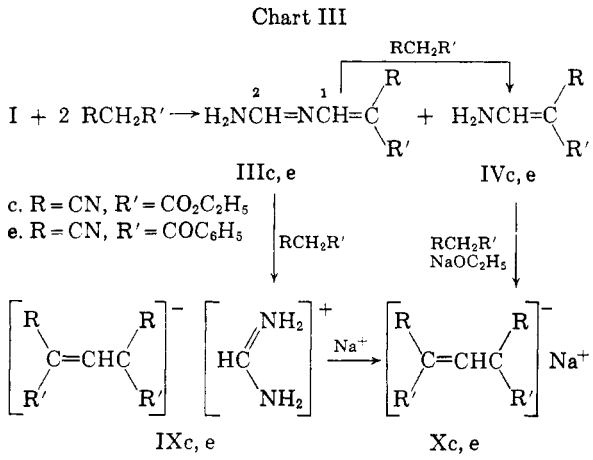
(10) L. Claisen, *Ann.*, 297, 1 (1897).

(11) H. Wieland and E. Dorrer, *Ber.*, 58, 818 (1925).

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

(13) Ref. 4 reported only IVc from the uncatalyzed reaction.

Chart III



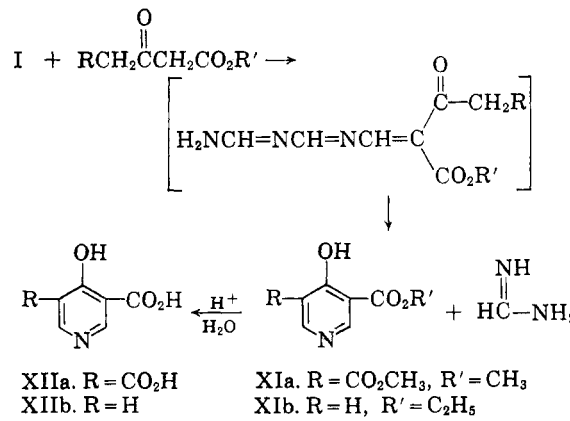
ently be cleaved by further reaction with ethyl cyanoacetate at either C-1 or C-2 depending upon the conditions. Thus, in the absence of base, attack occurs at C-1 leading to the formamidine salt IXc, while in the base-catalyzed reaction IIIc is cleaved in the usual manner by attack of the reagent at C-2, leading to two more equivalents of IVc. When a full equivalent of base is used, however, IVc can react further with the active methylene reagent to give Xc, as was demonstrated in a separate experiment. A partial explanation for the failure of the pyrimidine synthesis in this instance became apparent when it was found that IVc did not react with *s*-triazine under conditions which were successful in converting IVa to Va. The reason for this failure is not clear. Further support for the reaction sequence shown in Chart III is found in the yield data.[5,14]

In two instances the reaction of *s*-triazine with active methylene compounds containing a second acidic methyl or methylene group led to pyridines. This behavior was shown by 1,3-dicarbomethoxyacetone and ethyl acetoacetate, which afforded the 4-hydroxypyridines XIa and XIb, respectively, under conditions which normally gave pyrimidines. Interestingly, Kreutzberger and Grundmann[4] obtained a different pyridine, namely the 3,5-dicarbethoxy-2,6-dimethyl derivative, by heating ethyl acetoacetate with I in the absence of base or solvent.

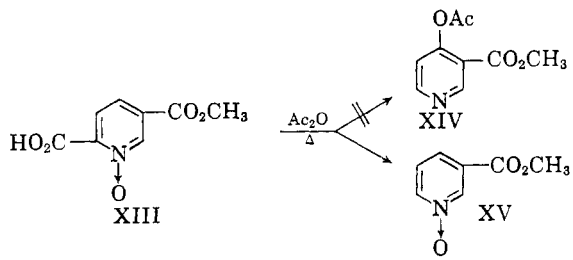
The reactions in which hydroxypyridines are formed can be considered to proceed through an intermediate analogous to II, in which nucleophilic attack can now occur intramolecularly with elimination of formamidine, thus forming a stable six-membered ring. Other more complex pathways are also possible.

Compound XIb was characterized by hydrolysis to 4-hydroxynicotinic acid (XIIb), which in turn was decarboxylated to 4-hydroxypyridine. The acid

(14) For example, in the uncatalyzed reaction between I and benzoylacetonitrile, the predicted yields of IXe and IVe are 67% and 33%, respectively, if IIIe is cleaved preferentially at C-1. This is in good agreement with the 59% and 29% yields obtained experimentally.



XIIb was recently described by Peterson,[15] who claimed to have prepared it by treatment of the *N*-oxide XIII with acetic anhydride, followed by hydrolysis of the product XIV. As the infrared spectrum of our sample of XIIb did not agree with the reported absorption,[15] we were led to repeat the reaction sequence as described by Peterson and have found his structure assignments to be erroneous. Thus, the product obtained by heating XIII with acetic anhydride proved to be methyl nicotinate *N*-oxide (XV) rather than XIV.[16] Hydrolysis then gave nicotinic acid *N*-oxide, identified by comparison with an authentic sample, rather than XIIb.[17]



One example of a second mode of pyridine formation was observed in the reaction of *s*-triazine with ethyl 2-cyanoacetimidate hydrochloride. Although closely related imidate hydrochlorides led to pyrimidines in all other cases studied,[1] the product in this instance was assigned the structure 3,5-dicyano-2,6-diethoxypyridine (XVI). This reaction apparently proceeded through a glutacononitrile intermediate, which then cyclized to XVI with loss

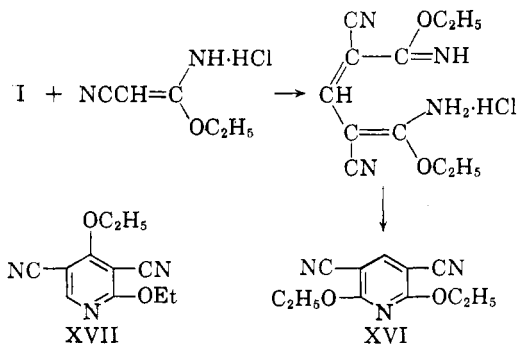
(15) M. L. Peterson, *J. Org. Chem.*, **25**, 565 (1960).

(16) For further examples of the facile decarboxylation of 2-carboxypyridine *N*-oxides in the presence of acetic anhydride, see (a) W. Sauermilch, *Arch. Pharm.*, **293**, 452 (1960), and (b) V. Boekelheide and W. L. Lehn, *J. Org. Chem.*, **26**, 428 (1961).

(17) (a) The product obtained upon reaction of the supposed XIV with water,[15] which was claimed to be the methyl ester of XIIb, was presumably an impure sample of the starting XV, on the basis of the analytical and spectral data reported; (b) The identification of this product as nicotinic acid *N*-oxide has also been reported very recently by T. Wieland, C. Fest, and G. Pfleiderer, *Ann.*, **642**, 163 (1961).

of ammonium chloride. Such a ring closure reaction would be a simple variation of a well known pyridine synthesis.[18]

An alternative structure, XVII, was also considered, as a plausible mechanism can also be written for its formation. The assignment of structure XVI is based primarily on the nuclear magnetic resonance spectrum, which indicated that the two ethyl groups were identical and in which the ring hydrogen absorption appeared at 2.0 τ.[19,20]



From the foregoing discussion, it is evident that the type of product obtained from the reaction of s-triazine with an active methylene compound is dependent upon the relative rates of several competing reactions. As a result of this competition, the course of the reaction can be drastically altered by apparently subtle changes in the nature of the active methylene reagent or in the experimental conditions.

It is interesting to compare these reactions of s-triazine with the corresponding reactions of formamidine described in the literature. Both malononitrile[21] and 3-amino-2-cyanoacrylonitrile (IVa)[22] react with formamidine to give 4-amino-5-cyanopyrimidine (Va). Similarly, the condensation of ethyl cyanoacetate with formamidine parallels that with s-triazine in that products IVc and Xc are formed, depending upon the amount of base used.[22] These reactions of formamidine may or may not proceed through the same intermediates as do those with s-triazine.[23] In contrast, diethyl malonate and formamidine give 4,6-dihydroxypyrimidine,[22] a product which is not obtained from the ester and I.

(18) E. L. Little *et al.*, *J. Am. Chem. Soc.*, **80**, 2832 (1958).

(19) Determined as a 10% solution in $CDCl_3$.

(20) On the basis of the limited data available in the literature concerning the NMR spectra of pyridine derivatives, this appears to be a reasonable value for XVI, whereas the isomeric XVII would be expected to show the ring hydrogen at <1.0 τ. See A. Katritzky and J. Lagowski, *J. Chem. Soc.*, 43 (1961); and J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961), for the spectra of various pyridines.

(21) J. Baddiley, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 386 (1943).

(22) G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 388 (1943).

EXPERIMENTAL[24]

Reaction of s-triazine with malononitrile. A. In ethanol. To 10 ml. of absolute ethanol were added 2.0 g. (0.030 mole) of malononitrile and 1.6 g. (0.020 mole) of s-triazine.[25] The resulting mixture was shaken for a few minutes while heat was evolved and a bright yellow solid crystallized. The solid, *N-(2,2-dicyanovinyl)formamidine* (IIIa), was filtered and washed with ethanol. Yield 1.35 g. (37.5%), m.p. >300° dec., λ_{max}^{MeOH} 268 mμ (ε 12,700).

Anal. Calcd., for $C_5H_4N_4$: C, 49.99; H, 3.36; N, 46.65. Found: C, 49.95; H, 3.46; N, 46.94.

The infrared spectrum showed no bands attributable to the isomeric Va.

Evaporation of the filtrate gave a yellow solid which was triturated with benzene. This was crude *3-amino-2-cyanoacrylonitrile* (IVa), 1.75 g. (62.5%), m.p. 102–113°, contaminated by a small amount of unidentified impurity. Several recrystallizations from water gave a white product, m.p. 124–133°, but the m.p. could not be raised to the literature values[4,26,27] of 140° and 146°.

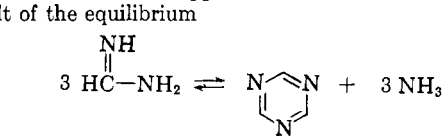
Anal. Calcd. for $C_4H_3N_3$: C, 51.61; H, 3.25. Found: C, 51.52; H, 3.63.

B. In dimethylformamide A solution of 1.30 g. of malonotrile (0.020 mole) and 0.80 g. (0.010 mole) of s-triazine in 5 ml. of dimethylformamide became warm within a few seconds after mixing the reagents. After standing for 15 min., the solvent was distilled at reduced pressure and the residue was triturated with benzene to give 1.67 g. (91%) of crude IVa., m.p. 105–123°. Three recrystallizations from water raised the m.p. to 131–138°, but further recrystallization did not increase it. The infrared spectrum was identical with a sample prepared as above.

4-Amino-5-cyanopyrimidine (Va). *A.* A 0.50-g. sample of IIIa was added to 25 ml. of water and the mixture was heated on the steam bath for 20 minutes and allowed to cool. Filtration afforded 0.45 g. (90%) of Va as tan needles, m.p. 255–256°, lit.[21,4] m.p. 250° and 255–256°.

B. A solution of 0.93 g. (0.010 mole) of IVa and 0.85 g. (0.010 mole) of I in 10 ml. of ethanol containing 50 mg of sodium ethoxide was refluxed for 3 hours and allowed to cool. The pyrimidine Va was obtained as a brown solid, 0.90

(23) The instability of formamidine in solution has occasionally not been appreciated. When the free base is liberated from the hydrochloride by treatment with sodium ethoxide in ethanol, ammonia is evolved within a short time. We have found that, after standing for a few hours, the solution contains an appreciable amount of s-triazine, a result of the equilibrium



Linear condensation products are also presumably present. It does not necessarily follow that the reactions of formamidine with malononitrile or ethyl cyanoacetate proceed through s-triazine as an intermediate, as the rates of the competing reactions are not known.

(24) Melting points are uncorrected. Microanalyses were performed under the direction of Dr. J. A. Kuck or by Galbraith Microanalytical Laboratories. Infrared, NMR, and ultraviolet spectra were obtained under the supervision of Mr. N. B. Colthup, Dr. J. E. Lancaster, and Dr. R. C. Hirt, respectively, each of whom also aided in the interpretation.

(25) (a) L. E. Hinkel and R. T. Dunn, *J. Chem. Soc.*, 1834 (1930). (b) C. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc.*, **76**, 632 (1954). (c) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 2778 (1961).

(26) T. Passalacqua, *Gazz. chim. ital.*, **43**, II, 566 (1913).

(27) O. Diels, H. Gärtner, and R. Kaack, *Ber.*, **55**, 3439 (1922).

g. (75%), m.p. 244–246° dec. Recrystallization from water gave tan needles, m.p. 255–256°, identical with the sample obtained as above.

C. To 5 ml. of absolute ethanol were added in rapid succession 1.65 g. (0.025 mole) of crystalline malononitrile, 2.0 g. (0.025 mole) of I, and 0.1 g. (0.002 mole) of sodium methoxide. The resulting mixture was shaken until all of the starting materials had dissolved and then refluxed for 3 hours. The product Va was obtained as a brown solid, 2.0 g., m.p. 249–251° dec. The filtrate upon standing overnight yielded another 0.40 g., m.p. 245–248° dec., for a total of 2.4 g. (80%). Recrystallization from water afforded pure material m p 255–256°.

4-Acetamido-5-cyanopyrimidine, m.p. 124–125°, was prepared by acetylation of Va with acetic anhydride according to the literature procedure.[21] This product had been previously assigned the structure of a ring-opened isomer,[21,28] but no evidence was published to support this contention. The infrared and ultra-violet spectra were in complete agreement with the normal pyrimidine structure; λ_{max}^{Nujol} 3.05, 4.48, 5.87, 6.3 (unresolved multiplet), and 12.8 μ. λ_{max}^{MeOH} 250 mμ (ϵ 11,670).

Preparation of 4-hydroxy- and 4-mercaptopyrimidines—General. In general, equimolar amounts of sodium ethoxide, the active methylene compound, and *s*-triazine were mixed in that order in absolute ethanol and the solution was refluxed until it had become quite dark (30 min. to two hours.). The ethanol was removed at reduced pressure and the residue was dissolved in the minimum amount of water. Acidification of the cold aqueous solution caused crystallization of the pyrimidine, which was then recrystallized from water. Exceptions to this procedure are described under the individual compounds.

5-Carbethoxy-4-hydroxypyrimidine (VIa). The above procedure, when applied to 2.0 g. of diethyl malonate, gave 0.89 g. (42%) of VIa, m.p. 189.5–190.5°. After a second recrystallization the m.p. was 191–192°. Reported values[4,29] are 185° and 194–195°. Contrary to the literature report,[4] no difficulty was encountered in the conversion of the sodium salt to the free pyrimidine by the standard procedure.

5-Carbamoyl-4-hydroxypyrimidine (VIb) was similarly prepared from 1.25 g. of malonamide. The yield was 1.25 g. (69%), m.p. 273–275° dec. One further recrystallization afforded an off-white analytical sample, m.p. 276–278° dec., which analyzed as a hemihydrate despite previous drying *in vacuo* at 100°.

Anal. Calcd. for $C_5H_5N_3O_2 \cdot {}^1/_2H_2O$: C, 40.54; H, 4.08; N, 28.37. Found: C, 40.69; H, 4.37; N, 28.35.

5-Carboxy-4-hydroxypyrimidine was obtained by hydrolysis of either the ester VIa or the amide VIb in hot 20% hydrochloric acid. After two recrystallizations from water the acid had m.p. 236–237° dec., in agreement with the literature values of 238° dec.[29] and 236–237° dec.[30]

4-Hydroxy-5-phenylpyrimidine (VIc). The general procedure, applied to 2.50 g. of phenylacetamide, gave 1.45 g. (46%) of VIc, m.p. 165–170°. Two further recrystallizations afforded pale yellow prisms, m.p. 176–178°. Lit.[31] m.p. 173–174°.

5-Cyano-4-mercaptopyrimidine (VII). From 5.0 g. of 2-cyanothioacetamide[32] there was obtained 6.2 g. (90%) of VII as a brownish-orange solid, m.p. >300°. This product was difficult to purify because of its very low solubility in most common solvents. The analytical sample was obtained by dissolving a portion in dilute aqueous ammonia, adding enough dilute hydrochloric acid to precipitate about half the product, which was discarded, and then acidifying the filtrate. In this manner a purer second crop of brownish-orange solid, m.p. >300°, was obtained.

Anal. Calcd. for $C_5H_3N_3S$: C, 43.78; H, 2.20; N, 30.63; S, 23.38. Found: C, 43.28; H, 2.38; N, 30.47; S, 23.63.

Treatment of the above material with one equivalent of methyl iodide in dilute aqueous sodium hydroxide gave *5-cyano-4-methylthiopyrimidine*, m.p. 92–93.5° from ethanol. It was identical with the product obtained previously[1] from reaction of I with methyl 2-cyanothioacetimidate hydrochloride.

5-Cyano-4-phenylpyrimidine (VIII). A solution of 8.1 g. (0.10 mole) of I and 14.5 g. (0.10 mole) of benzoylacetonitrile in 50 ml. of ethanol was treated with 1.1 g. (0.020 mole) of sodium methoxide and refluxed for 1.5 hours. Upon chilling, 5.6 g. (31%) of VIII crystallized as yellow needles, m.p. 95–96°. Recrystallization from ethanol gave colorless material of the same m.p.

Anal. Calcd. for $C_{11}H_7N_3$: C, 72.91; H, 3.89; N, 23.19. Found: C, 72.76; H, 3.92; N, 22.82.

4-Amino-5-carbamoylpyrimidine (Vb). A solution of 2.7 g. of sodium methoxide (0.050 mole), 4.2 g. of 2-cyanoacetamide (0.050 mole), and 4.3 g. of I (0.053 mole) in 40 ml. of anhydrous methanol was refluxed for 15 minutes while the product crystallized. After cooling, the yellow solid was filtered and washed with fresh methanol. The yield was 3.8 g. (55%), m.p. 252–259° dec. One recrystallization from water afforded white crystals, m.p. 258–261° dec. The reported[33] m.p. is 254–256°.

Ethyl 3-amino-2-cyanoacrylate (IVc). A solution of 2.25 g. (0.020 mole) of ethyl cyanoacetate and 1.70 g. (0.021 mole) of I in 7 ml. of ethanol, to which 0.05 g. (0.001 mole) of sodium methoxide had been added, was refluxed for 30 min. and evaporated to dryness. Crystallization of the residue from water gave 2.75 g. (98%) of crude IVc, m.p. 112–121°. One recrystallization from water gave 2.20 g., m.p. 124–129°. Two further recrystallizations from ethyl acetate raised the m.p. to 134.5–135.5°. The literature values[4,12,22,34] range from 130° to 140.5–142.5°.

Compound IVc did not react with *s*-triazine under the conditions used to convert IVa to Va.

Diethyl 2,2'-dicyanoglutaconate, formamidine salt (IXc). To a solution of 4.50 g. (0.040 mole) of ethyl cyanoacetate in 10 ml. of ethanol was added 1.70 g. (0.021 mole) of I. After the initial exotherm had subsided, the resulting solution was kept at 25° for four hours and then refluxed for 30 minutes. The solvent was removed to give a crystalline residue identified as a mixture of IVc and IXc by infrared analysis. Recrystallization from ethyl acetate–ether followed by a second recrystallization from ethyl acetate afforded 2.05 g. (36%) of pure IXc as a white solid, m.p. 169–170°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4 \cdot CH_4N_2 \cdot {}^1/_2H_2O$: C, 49.81; H, 5.92; N, 19.37. Found: C, 50.03; H, 5.93; N, 19.05.

Treatment of a 100-mg. sample of IXc with picric acid in ethanol gave a mixture of products from which formamidine picrate was separated by trituration with ethanol at 25°. The resulting sample had m.p. 240–243° dec. and was identical with respect to infrared spectrum and mixed m.p. with an authentic sample,[12] m.p. 242–244° dec., lit.[12,35] m.p. 251–253° and 246–248° dec.

Addition of hydrochloric acid to a dilute aqueous solution of IXc caused crystallization of the free *diethyl 2,2'-dicyanoglutaconate*. Two recrystallizations from acetone gave yellow needles, m.p. 177–178° dec., identical with a sample ob-

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tained by a literature procedure.[22] Reported values[36,37] range from 178–179° to 187–188°.

Sodium diethyl 2,2'-dicyanoglutaconate (Xc). *A.* When a sample of the formamidine salt IXc was dissolved in hot water and an excess of sodium chloride was added, the sodium salt Xc crystallized on cooling. It was recrystallized once from water and twice from ethyl acetate, m.p. 273–275° dec., and was identical by mixed m.p. and infrared comparison with authentic samples prepared by each of two literature methods.[22,37] This product is reported to melt[36,38] at 263–265° and to be a dihydrate.[36,37]

B. A solution of 2.25 g. (0.020 mole) of ethyl cyanoacetate and 1.60 g. (0.020 mole) of I in 25 ml. of ethanol containing 0.020 mole of sodium ethoxide was refluxed for 20 min. and evaporated to dryness. The resulting solid was washed with a little cold water to give 1.8 g. (61%) of Xc m.p. >250° dec. One recrystallization from ethanol afforded 1.45 g., m.p. 270–272° dec., identified by comparison with samples prepared as above.

C. A solution of 1.1 g. (0.010 mole) of ethyl cyanoacetate and 1.4 g. (0.010 mole) of IVc in 15 ml. of ethanol containing 0.010 mole of sodium ethoxide was refluxed for 20 min. and evaporated to dryness. Recrystallization of the residue from water resulted in 1.60 g. (55%) of Xc, m.p. 263–265° dec., which after a second recrystallization had m.p. 273–275° dec. This sample was identical with those described above.

Reaction of s-triazine with benzoylacetonitrile in absence of base. A mixture of 1.45 g. (0.010 mole) of benzoylacetonitrile and 0.80 g. (0.010 mole) of I in 10 ml. of ethanol was shaken for several minutes until a clear solution was obtained. After standing overnight the solution was chilled to give 0.50 g. of yellow crystals, m.p. 168–170°. Evaporation of the filtrate and recrystallization of the residue from ethyl acetate gave another 0.55 g., m.p. 170–172°, for a total of 1.05 g. (59%) of *2,2'-dibenzoylglutaconononitrile formamidine salt* (IXe). Further recrystallization from acetonitrile afforded yellow crystals, m.p. 177–178°.

Anal. Calcd. for $C_{19}H_{12}N_2O_2 \cdot CH_4N_2 \cdot {}^1/_2H_2O$: C, 67.97; H, 4.85; N, 15.85. Found: C, 67.95; H, 5.08; N, (different sample) 15.82.

Compound IXe was converted to the corresponding sodium salt Xe by reaction with aqueous sodium chloride. The resulting pale yellow needles had m.p. >300°.

Anal. Calcd. for $C_{19}H_{11}N_2O_2Na \cdot 2H_2O$: C, 63.69; H, 4.22; N, 7.82. Found: C, 64.26; H, 3.86; N, 8.02.

The ethyl acetate filtrate from above was diluted with a little ether to throw out some dark gum from which the solution was decanted. Evaporation to dryness gave 0.50 g. (29%) of crude *3-amino-2-benzoylacrylonitrile* (IVe), m.p. 118–124°. Recrystallization from ethanol-water yielded pale yellow crystals, m.p. 133–135°.

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.67; H, 4.67; N, 16.17.

3-Amino-2-cyanoacrylamide (IVb). A solution of 4.2 g. (0.050 mole) of cyanoacetamide, 4.3 g. (0.053 mole) of I and 0.20 g (0.0037 mole) of sodium methoxide in 40 ml. of methanol was kept at 25° for four hours. The crude IVb was isolated from the dark reaction mixture as a greenish solid, 4.55 g., m.p. *ca.* 150–170°. Another 0.55 g., m.p. 176–180°, was obtained by evaporation of the mother liquor and recrystallization of the residue from water. Recrystallization of the first crop from water afforded 3.25 g., m.p. 174–178°, for a total of 3.80 g. (68%) of recrystallized material.

Two further recrystallizations from water using charcoal gave a cream colored analytical sample, m.p. 182–183°.

Anal. Calcd. for $C_4H_5N_3O$: C, 43.24; H, 4.54; N, 37.83. Found: C, 42.97, H, 4.16, N, 38.20.

3-Aminomethylene-2,4-pentanedione (IVd). A solution of 5.0 g. (0.050 mole) of acetylacetone, 4.0 g. (0.050 mole) of I, and 0.3 g. (0.005 mole) of acetic acid in 15 ml. of absolute ethanol was refluxed for four hours. The solution was concentrated, chilled, and filtered to give 3.75 g. (59%) of crude IVd, m.p. 120–137°. One recrystallization from ethyl acetate afforded 2.85 g. (44%), m.p. 142–144°, lit. m.p. 144°[10,11] and 145–146°.[4]

Compound IVd was also the only isolable product from a similar reaction in the presence of alkoxide.

3,5-Dicarbomethoxy-4-hydroxypyridine (XIa). To a solution of 1.75 g. (0.010 mole) of 1,3-dicarbomethoxyacetone and 0.55 g. (0.010 mole) of sodium methoxide in 15 ml. of dry methanol was added 0.80 g. (0.010 mole) of I. After the initial exotherm, during which a white solid began to crystallize, the mixture was refluxed for 10 minutes. The solid was filtered, washed with water, and was recrystallized from acetic acid. This yielded 1.25 g. (59%) of XIa, m.p. 260–262°. A second recrystallization raised the m.p. to 262–264°.

Anal. Calcd. for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63· Found: C, 51.22; H; 4.58; N, 6.41.

Hydrolysis with hot 6 *N* hydrochloric acid gave the corresponding diacid XIIa, m.p. 317–318° dec., lit.[39] m.p. 315° dec.

Ethyl 4-hydroxynicotinate (XIb). The general procedure for synthesis of hydroxypyrimidines described earlier, when applied to 3.20 g. of ethyl acetoacetate gave 1.05 g. (26%) of XIb, m.p. 223–225°. Two further recrystallizations yielded a white analytical sample, m.p. 228–229.5°.

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.40; H, 5.85; N, 8.36.

Acid hydrolysis of a small sample gave *4-hydroxynicotinic acid* (XIIb), m.p. 265–267° dec., from water. Lit.[40,41] m.p. 250° dec. and 249° dec. Compound XIIb was decarboxylated by heating at 280–290° for several minutes. *4-Hydroxypyridine* was isolated as the monohydrate, identified by infrared comparison with an authentic sample.

Reaction of 5-carbomethoxypicolinic acid N-oxide (XIII) *with acetic anhydride.* Compound XIII, m.p. 146–147°, was prepared and subjected to treatment with acetic anhydride according to the literature procedure.[15] After distillation of the acetic anhydride the residue was recrystallized three times from benzene–petroleum ether giving a tan solid, m.p. 97–99° identical in all respects with an authentic sample[42] of methyl nicotinate *N*-oxide (XV), prepared starting from nicotinic acid. Peterson[15] reported m.p. 100–101.5° for his product, while authentic XV is reported[42] to have m.p. 97°.

Hydrolysis of the above sample in hot 20% hydrochloric acid gave nicotinic acid *N*-oxide, m.p. 249–253° dec., identical with an authentic sample,[42] and having the same characteristic infrared absorption as reported by Peterson[15] for his product, m.p. 245–247° dec.

3,5-Dicyano-2,6-diethoxypyridine (XVI). Ethyl 2-cyanoacetimidate hydrochloride[43] (7.5 g., 0.050 mole) and 4.0 g. (0.050 mole) of I were added in rapid succession to 10 ml. of ethanol. The resulting mixture was shaken for five minutes with occasional cooling in an ice bath to keep the temperature below 30°. After standing overnight, the mixture was chilled and filtered giving 3.8 g. (69%) of XVI as a pale

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yellow solid, m.p. 145–148°. Two recrystallizations from ethanol afforded pale yellow needles, m.p. 144–145°.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.34; H, 5.14; N, 19.20.

Attempted acidic or basic hydrolysis to the known dihydroxydiacid was unsuccessful because of the great degree of stability shown by the nitrile groups.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, ASSIUT UNIVERSITY]

2-Arylnaphthoxazoles and Some Other Condensed Oxazoles

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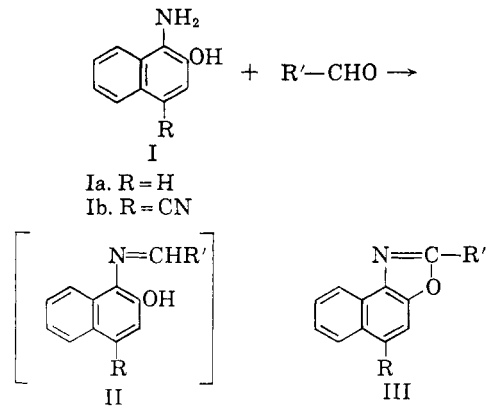
2-Arylnaphth(1,2-*d*)oxazoles (III. R = H) and their 5-cyano derivatives (III. R = CN) were synthesized by interaction of 1-amino-2-naphthol and 1-amino-2-hydroxy-4-cyanonaphthalene (1b) with aromatic aldehydes. The products exhibited strong violet or bluish-violet fluorescence in solutions. 2-Mercapto-5-cyanonaphth(1,2-*d*)oxazole (IV) was obtained by the action of potassium methyl xanthate on 1b. Interaction of 1-nitroso-2-naphthol with benzylamine gave a naphthoxazole, considered to be 2-phenyl-5-benzylaminonaphth(1,2-*d*)oxazole (VIII). Other condensed oxazoles—namely, benzoxazoles (X), benzdioxazoles (XI. R = H), 4,8-dichlorobenzdioxazoles (XI. R = Cl), phenanthroxazoles (XII), and chrysenoxazoles (XIII)—were obtained in good yields by direct fusion of aromatic aldehydes with suitable amino or imino compounds.

Continuing our work on the synthesis of condensed oxazoles[1] for their use as bacteriostatic agents and as intermediates for azo dyes, the preparation of naphthoxazoles and other condensed oxazoles was undertaken.

The chemistry of naphthoxazoles has received little attention before,[2,3] and in the following investigation, 2-arylnaphth(1,2-*d*)oxazoles[4] (III. R-H) and their 5-cyano derivatives (III. R = CN) were synthesised by the action of aromatic aldehydes on 1-amino-2-naphthol hydrochloride and 1-amino-2-hydroxy-4-cyanonaphthalene (Ib),[5] in the absence of solvents and basic catalysts. The reaction was negative with aliphatic aldehydes.

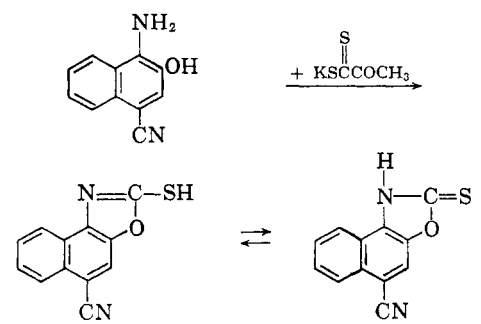
The resulting naphthoxazoles and cyanonaphthoxazoles possessed similar properties and they were characterized as follows: Their color ranged from white to pale yellow; they showed violet to bluish violet fluorescence in the organic solvents; they were remarkably stable toward acids and bases, and they sublimed unchanged in vacuum. These properties when combined with the analytical results, confirmed the oxazole structure (III. R = H or CN) assigned to these products.

Formation of these oxazoles is expected to take place through an intermediate Schiff's base (II), which is likely to undergo oxidation and instantaneous cyclization forming 2-arylnaphth(1,2-*d*)oxazoles. The reaction can be illustrated as follows:



IIIa. R = H; R' = C_6H_5; *o*-OHC_6H_4; *p*-$CH_3OC_6H_4$
IIIb. R = CN; R' = C_6H_5; *p*-$CH_3OC_6H_4$; $C_6H_5CH{=}CH$; $CH_2O_2C_6H_3$

The aminonaphthols (Ia and Ib) were utilized for the preparation of mercaptonaphthoxazoles by interaction with potassium methyl xanthate. The reaction proceeded only with the cyanoaminonaphthol (Ib) giving a highly stable light yellow product which sublimed unchanged in vacuum, dissolved readily in alkalies, and precipitated unchanged on acidification. The substance showed no fluorescence in solutions. The analytical results were in full agreement with the mercaptocyanonaphthoxazole (IV).



IV

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(4) These are also known as B-naphthoxazoles; *cf.* N. I. Fisher *et al.*, *J. Chem. Soc.*, 962 (1934).
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