Studies on the Pyrimidine Derivatives. XXIX.[1,2] Reactions of 3-Ethoxy-2-methoxymethylenepropionitrile and 3-Ethoxy-2-ethoxymethoxymethylpropionitrile with Urea and Thiourea Derivatives

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3-Ethoxy-2-methoxymethylenepropionitrile (I) or its acetal (II) undergo condensation with urea, N-substituted ureas, thiourea, and N-substituted thiourea. The condensation has been carried out by heating the enol ether propionitrile (I) or acetal propionitrile (II) in ethanol solution, in the presence of hydrochloric acid, with urea to obtain directly 5-cyano-2-oxo-1,2,3,4-tetrahydropyrimidine (III), with N,N′-dimethylurea to yield 5-cyano-1,3-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine (IX), with N-methylurea to give a mixture of 5-cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (X) and its isomeric 3-methyl compound (XI), which was separated into each isomer, and with N-phenylurea to obtain exclusively the 1-phenyl compound (XV). Further dehydrogenation of these compounds made possible a new synthetic route to pyrimidines. The condensation was also carried out with thiourea and I or II in alcoholic solution in the presence of hydrochloric acid to obtain 5-cyano-2-oxo-6H-2,3-dihydro-1,3-thiazine (XVIII) and with N-phenylthiourea to give XVIII and aniline. Elucidation of the structures of these compounds is described.

We have previously reported the reaction of acetamidine[3] and related amidines[4] with 3-ethoxy-2-methoxymethylenepropionitrile (I) to give 2-substituted 4-amino-5-ethoxymethylpyrimidines, and with 3-ethoxy-2-ethoxymethoxymethylpropionitrile (II) to yield 2,7-disubstituted 5,6-dihydropyrimido[4,5-*d*]pyrimidines.[3,4] This paper deals with the reaction of I or II with urea, N-substituted ureas, thiourea, and N-substituted thiourea (see Scheme I).

Reaction of I, a mixture of geometrical isomers,[5] with urea was carried out in ethanol solution in the presence of hydrochloric acid. The base-catalyzed condensation of aldehyde nitrile derivatives with urea is a standard synthesis of cytosine derivatives.[6] However, in this case a product III, $C_5H_5N_3O$, was obtained in 42.6% yield by acid-catalyzed reaction, and no evidence for the formation of other products was shown by thin-layer chromatography of the filtrate. The infrared spectrum of III shows NH bands, a conjugated C≡N band, and an amide I band. Hydrolysis of III in concentrated hydrochloric acid gave the amide IV. Acetylation with acetic anhydride afforded the diacetate V. The proton magnetic resonance spectrum[7] of V (Table I) shows two singlet signals (3H) at τ 7.32 and 7.40 arising from the protons of 1- and 3-N-acetyl groups, respectively. The signals of the protons of C-4 methylene and C-6 methylidyne groups appear at τ 5.56 (2H) and 2.05 (1H), respectively; the former is split into a doublet and the latter into a triplet due to the spin coupling (J = 1.0 c.p.s.) with each other. These results indicate that III can be formulated as 5-cyano-2-oxo-1,2,3,4-tetrahydropyrimidine. By the action of bromine in acetic acid solution, III was dehydrogenated to give 5-cyano-2-oxo-1,2-dihydropyrimidine (VI), which was converted into 5-cyano-2-chloropyrimidine (VII) on treatment with phosphorus oxychloride. Amination of VII gave the 2-amino derivative VIII. This compound VIII was identified as 2-amino-5-cyanopyrimidine by comparison of its infrared and ultraviolet spectra with those of an authentic sample.[8] Thus the structure of III was established. It should be noted that this synthesis is useful in obtaining 2-substituted 5-cyanopyrimidines.

Reaction of I with N,N′-dimethylurea in ethanol solution in the presence of hydrochloric acid gave a product IX, $C_7H_9N_3O$, in 56.3% yield. Infrared spectrum of IX shows a conjugated C≡N band and C=O band, but no NH band is shown. The n.m.r. spectrum of IX exhibits the signals of the protons of two N-methyl, C-4 methylene, and C-6 methylidyne groups as shown in Table I. Thus IX is formulated as 5-cyano-1,3-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine.

Reaction of I with N-methylurea in ethanol solution in the presence of hydrochloric acid afforded a product of m.p. 187–188°, $C_6H_7N_3O$, which showed two spots on a thin-layer chromatogram and which could be converted into a mixture of acetates. The n.m.r. spectrum of this mixture of acetates consists of four pairs of signals of N-acetyl, N-methyl, C-4 methylene, and C-6 methylidyne protons whose respective relative integrated intensities are about 3:2. Thus, this product was revealed to be a mixture of 3-acetyl-5-cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XII) and the 3-methyl isomer XIII in a ratio of 3:2. This mixture was subjected to column chromatography on alumina and two crystalline products of m.p. 94° (XII) and m.p. 118° (XIII) were obtained separately. The assignment of the structures of these compounds was made as follows. The n.m.r. spectrum of N,N′-diacetyl compound V shows the signals of C-4 methylene and C-6 methylidyne protons at lower fields than those of the protons of N,N′-dimethyl compound IX (see Table I). Therefore, in XII and XIII these protons resonating at lower fields will be situated at positions adjacent to the N-acetyl group. The spectrum of XII shows the signals of the N-acetyl and C-6

(1) A part of this paper has been delivered at the 19th congress of I.U.P.A.C., London, July 10–17, 1963.

(2) Part XXVIII: *Chem. Pharm. Bull.* (Tokyo), **12**, 398 (1964).

(3) A. Takamizawa, K. Ikawa, and K. Tori, *Yakugaku Zasshi*, **78**, 647 (1958); A. Takamizawa, K. Tokuyama, and K. Tori, *Bull. Chem. Soc. Japan*, **32**, 188 (1959).

(4) A. Takamizawa and K. Hirai, *Chem. Pharm. Bull.* (Tokyo), **12**, 393 (1964).

(5) A. Takamizawa, K. Hirai, and K. Tori, *ibid.*, **11**, 1212 (1963).

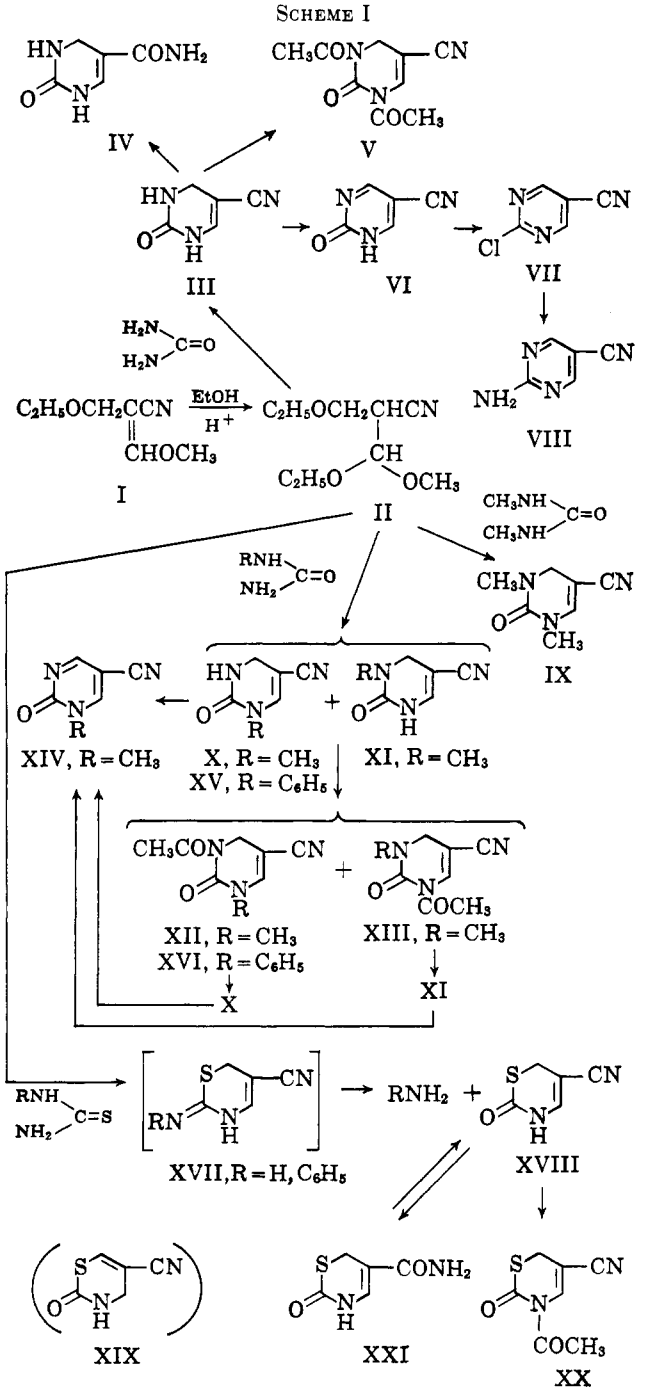
(6) D. J. Brown, "The Pyrimidines," John Wiley and Sons, Inc., New York, N. Y., 1962, pp. 59–61.

(7) All the n.m.r. spectra were taken with a Varian A-60 spectrometer on about 10% solution in deuteriochloroform containing about 1% tetramethylsilane (TMS) as an internal reference. Chemical shifts are expressed in τ-values and coupling constants are in c.p.s. Accuracy limits are about τ ±0.02 for chemical shifts and about ±0.3 c.p.s. for coupling constants.

(8) J. P. English, J. H. Clark, R. G. Shepard, H. W. Marson, J. Krapcho, and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **68**, 1039 (1946).

(9) T.l.c.: alumina plate, ethyl acetate solvent, detected by iodine vapor.

SCHEME I



methylidyne protons at higher fields and those of the N-methyl and C-4 methylene protons at lower fields than does that of XIII. Accordingly, the C-4 methylene in XII should be situated at a position adjacent to to the N-acetyl group. Therefore, XII can be formulated as 3-acetyl-5-cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine. Conversely, XIII can be formulated as the 3-methyl isomer. Hydrolyses of XII and XIII gave 5-cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (X) and the 3-methyl isomer XI, respectively. A mixture of X and XI was dehydrogenated by the action of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane solution to give 5-cyano-1-methyl-2-oxo-1,2-dihydropyrimidine (XIV) in good yield. It should be noted that this synthesis is a useful method for obtaining new N-substituted 5-cyano-2-oxopyrimidines. The dehydrogenation of X and XI was made separately to yield the same product XIV.

N-Phenylurea reacted with I in ethanol solution in the presence of hydrochloric acid to give the product XV, $C_{11}H_9N_3O$, in 42.6% yield. The n.m.r. spectrum of the acetate of XV shows that this product is not a mixture and that the acetate XVI can be formulated as 3-acetyl-5-cyano-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine. In this reaction the 3-phenyl isomer was not obtained.

Reaction of I with thiourea was also carried out in ethanol solution in the presence of hydrochloric acid and the product XVIII, $C_5H_4N_2OS$, and ammonium chloride were obtained. This product XVIII was hydrolyzed in concentrated hydrochloric acid to give the amide XXI which was converted into the original XVIII by the action of phosphorus oxychloride. Acetylation of XVIII gave monoacetate XX. These facts suggest that this compound XVIII is 5-cyano-2-oxo-6H-2,3-dihydro-1,3-thiazine or its isomeric structure XIX. The n.m.r. spectrum of XX shows a singlet (3H) at τ 7.38 due to the N-acetyl group, a doublet (2H, J = 0.8 c.p.s.) at τ 6.23 due to the C-6 methylene protons, and a triplet (1H, J = 0.8 c.p.s.) at τ 2.07 due to the C-4 methylidyne proton. The spectrum of XVIII shows a doublet (J = 0.8 c.p.s.) at τ 6.26, and a doubling triplet (J = 6.5, 0.8 c.p.s.) at τ 3.11, which changes into a triplet by the addition of a small amount of deuterium oxide to the solution examined.[10,11] These facts imply that the NH group is situated at a position adjacent to the C-4 methylidyne group. From all of these observations, XVIII was elucidated to be 5-cyano-2-oxo-6H-2,3-dihydro-1,3-thiazine. Similarly, the reaction of I with N-phenylthiourea in ethanol solution in the presence of hydrochloric acid gave XVIII and aniline hydrochloride. These products would result from hydrolysis of the probable 2-imino intermediate.

In a previous paper,[12] acid treatment of the enol ether nitrile I in ethanol was reported to give its acetal II. In the present cases, it is reasonable to assume that II is an intermediate in the reaction of I with ureas or thioureas in ethanol in the presence of hydrochloric acid. This assumption was supported by the facts that II reacted with urea, N,N′-dimethylurea, and thiourea to afford III, IX, and XVIII in 46.7, 56.3, and 24.3% yield, respectively. However, the possibility that a part of the nitrile I can directly react with these reagents to give products analogous to those obtained from the reaction with amidines cannot be excluded at this point.

It should be noted that the cyano group in I or II did not participate in the cyclization reaction with urea, in contrast to reaction with amidines.[3] Of much interest is the fact that the sulfur atom participated preferentially, probably in a thiol form, in the cyclization reaction

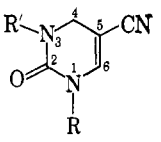
(10) This decoupling results from the proton exchanging of the N–H group [refer to H. M. Fales and A. T. Robertson, *Tetrahedron Letters*, **No. 3**, 111 (1962)].

(11) Spin coupling between –CH and –CONH– protons has frequently been reported [H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1959); G. V. D. Tiers and F. A. Bovey, *J. Phys. Chem.*, **63**, 302 (1957); K. Tori, *Ann. Rept. Shionogi Res. Lab.*, **12**, 114 (1962); and K. Tori and K. Kuriyama, *Chem. Ind.* (London), 1525 (1963)]. However, it is of considerable interest to note that =CH proton appreciably couples with a CONH proton.

(12) A. Takamizawa, K. Ikawa, and M. Narisada, *Yakugaku Zasshi*, **78**, 637 (1958).

TABLE I

N.M.R. SPECTRAL DATA IN DEUTERIOCHLOROFORM (10%)[a]

Compound	Chemical shift (τ) N-1-CH_3	N-3-CH_3	N-1-$COCH_3$	N-3-$COCH_3$	C-4-H[b]	C-6-H[b]
						
V, R = R′ = $COCH_3$			7.32	7.40	5.56 (d)	2.05 (t)
IX, R = R′ = CH_3	6.87	7.07			5.93 (d)	3.17 (t)
X, R = CH_3; R′ = H	6.88				5.87 (d)	3.20 (t)
XI, R = H; R′ = CH_3		7.08			5.95 (d)	3.15 (m)
XII, R = CH_3; R′ = $COCH_3$	6.77			7.46	5.57 (d)	3.08 (t)
XIII, R = $COCH_3$; R′ = CH_3		6.97	7.37		5.92 (d)	2.07 (t)
XVI, R = C_6H_5; R′ = $COCH_3$				7.42	5.43 (d)	2.95 (t)
						
XVIII,[c] R = H					3.11 (d-t)	6.26 (d)
XX, R = $COCH_3$				7.38	2.07 (t)	6.23 (d)

[a] Peak multiplicities are represented by d (doublet), t (triplet), m (multiplet), and d-t (doubling triplet). All methyl peaks are sharp singlets. [b] $J_{4,6}$ = 1.0 c.p.s. [c] Observed on a saturated solution.

of thioureas with I or II, and the expected product,[6] 4-amino-5-ethoxymethyl-2-mercaptopyrimidine, was not obtained.

Experimental

5-Cyano-2-oxo-1,2,3,4-tetrahydropyrimidine (III). A.—3-Ethoxy-2-methoxymethylenepropionitrile (I, 2.8 g.) and 1.2 g. of urea were added to a solution of 200 ml. of ethanol and 4 ml. of concentrated hydrochloric acid. The mixture was refluxed for 15 hr. and the product was collected after cooling, yielding 1.35 g. Recrystallization from water afforded 1.05 g. (42.6%) of colorless prisms, m.p. >300°, insoluble or slightly soluble in ether, ethyl acetate, chloroform, acetone, and ethanol; infrared spectrum (Nujol mull), 3250, 3100 (NH), 2230 (C≡N), and 1670 cm.$^{-1}$ (amide I); ultraviolet spectrum, $\lambda_{max}^{EtOH\ suspension}$ 276 mμ.

Anal. Calcd. for $C_5H_5N_3O$: C, 48.77; H, 4.10; N, 34.14. Found: C, 48.76; H, 4.41; N, 34.12.

B.—A solution of 1.2 g. of urea, 3.8 g. of II, and 4 ml. of concentrated hydrochloric acid in 200 ml. of ethanol was refluxed for 19 hr. as described above. The product (1.55 g.) was recrystallized from water to afford 1.15 g. (46.7%) of III.

5-Carboxamido-2-oxo-1,2,3,4-tetrahydropyrimidine (IV).—One gram of III was dissolved in 20 ml. of concentrated hydrochloric acid with slight warming and allowed to stand overnight at room temperature. The product was collected and recrystallized from water to afford 0.7 g. (61.1%) of colorless needles, m.p. 286–289° dec.; infrared spectrum shows no C≡N band; ultraviolet spectrum, λ_{max}^{EtOH} 240 mμ (log ε 4.38), 276 mμ (log ε 4.38).

Anal. Calcd. for $C_5H_7N_3O_2$: C, 42.56; H, 5.00; N, 29.78. Found: C, 42.47; H, 5.03; N, 29.82.

5-Cyano-1,3-diacetyl-2-oxo-1,2,3,4-tetrahydropyrimidine (V).—A mixture of 0.5 g. of III and 5 ml. of acetic anhydride was refluxed for 8 hr. The excess reagent was removed under reduced pressure and the residue was solidified on trituration with petroleum ether. Recrystallization from a mixture of ether and petroleum ether afforded 0.5 g. (61.4%) of colorless needles, m.p. 79–81°; infrared spectrum shows no NH band; ultraviolet spectrum, λ_{max}^{EtOH} 235 mμ (log ε 4.11).

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.36; N, 20.28. Found: C, 52.61; H, 4.59; N, 19.23.

5-Cyano-2-oxo-1,2-dihydropyrimidine (VI).—A mixture of 0.5 g. of III and 10 ml. of glacial acetic acid was heated and a solution of 0.65 g. of bromine in 2 ml. of glacial acetic acid was added to the mixture. The solution was refluxed for 3 hr., the product was collected and recrystallized from ethanol to afford 0.4 g. (80.3%) of colorless prisms, m.p. 260–262°; ultraviolet spectrum, λ_{max}^{EtOH} 257 mμ (log ε 4.40), 300 mμ (shoulder, log ε 2.97).

Anal. Calcd. for $C_5H_3N_3O$: C, 49.59; H, 2.50; N, 34.70. Found: C, 49.33; H, 2.69; N, 33.93.

2-Chloro-5-cyanopyrimidine (VII).—A mixture of 0.4 g. of VI, 4 ml. of phosphorus oxychloride, and 0.2 ml. of dimethylaniline was refluxed for 1 hr. The excess reagent was removed under reduced pressure, ice–water was added to the residue, and the mixture was extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate, the ether was removed, and the residue was recrystallized from a mixture of benzene and petroleum ether (b.p. 30–60°) to afford 0.3 g. (65.2%) of pale yellow needles, m.p. 130–132°; ultraviolet spectrum, λ_{max}^{EtOH} 228 mμ (log ε 4.10), 260 mμ (log ε 3.39).

Anal. Calcd. for $C_5H_2N_3Cl$: C, 43.05; H, 1.45; N, 30.17; Cl, 25.42. Found: C, 43.35; H, 1.81; N, 30.38; Cl, 25.44.

2-Amino-5-cyanopyrimidine (VIII).—A suspension of 0.5 g. of VII in 40 ml. of ethanol saturated with NH_3 was heated at 100° for 2 hr. On cooling, the product was collected and recrystallized from ethanol to afford 0.3 g. (69.7%) of colorless prisms, d.p. *ca.* 260°, lit.[8] d.p. 300–310°; infrared spectrum (Nujol mull), 3100, 2220, 1677, 1597, 1525, 1385, 1235, 1070, 969, 803, and 659 cm.$^{-1}$; ultraviolet spectrum, λ_{max}^{EtOH} 257 mμ (log ε 4.46), 296 mμ (log ε 3.54).

Anal. Calcd. for $C_5H_4N_4$: C, 50.00; H, 3.36; N, 46.65. Found: C, 50.08; H, 3.49; N, 46.09.

The infrared and ultraviolet spectra were identical with those of an authentic sample prepared by the method of English, *et al.*,[8] from 2-aminopyrimidine by bromination and subsequent cyanation.

5-Cyano-1,3-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine (IX). A.—A solution of 0.88 g. of N,N′-dimethylurea, 1.4 g. of I, and 2 ml. of concentrated hydrochloric acid in 100 ml. of ethanol was refluxed for 12 hr. The solution was concentrated *in vacuo*, neutralized with sodium bicarbonate solution, and extracted with chloroform. The chloroform extract, after drying over anhydrous magnesium sulfate, was evaporated to give the product which on recrystallization from a mixture of benzene and petroleum ether gave 0.85 g. (56.3%) of colorless pillars, m.p. 109°; infrared spectrum (Nujol mull), 2220 cm.$^{-1}$ (C≡N) and no NH band; ultraviolet spectrum, λ_{max}^{EtOH} 219 mμ (log ε 3.93), 290 mμ (log ε 3.92).

Anal. Calcd. for $C_7H_9N_3O$: C, 55.61; H, 6.00; N, 27.80. Found: C, 55.36; H, 6.16; N, 27.60.

B.—The solution of 0.88 g. of N,N′-dimethylurea, 1.9 g. of II, and 2 ml. of concentrated hydrochloric acid in 100 ml. of ethanol was refluxed for 6 hr. as described above and 0.85 g. (56.3%) of IX was obtained.

Reaction of I and N-Methylurea.—A solution of 2.82 g. of I, 1.48 g. of N-methylurea, and 2 ml. of concentrated hydrochloric acid in 100 ml. of ethanol was refluxed for 12 hr. It then was con-

centrated *in vacuo*, water was added to the residue, and the product was collected, yielding 1.6 g. (54.5%). Recrystallization from ethanol gave 1.25 g. (42.5%) of colorless prisms, m.p. 187–189°; t.l.c., R_f 0.33, 0.26.

Anal. Calcd. for $C_6H_7N_3O$: C, 52.54; H, 5.15; N, 30.64. Found: C, 52.67; H, 5.41; N, 30.35.

3-Acetyl-5-cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XII) and 1-Acetyl-5-cyano-3-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XIII).—A mixture of 4.5 g. of the product obtained above and 45 ml. of acetic anhydride was refluxed for 5 hr. After removing excess reagent, the residue was recrystallized from a mixture of benzene and petroleum ether to give 4.66 g. (85.0%) of colorless prisms, m.p. 75–78°.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.88; H, 5.25; N, 22.95.

This product (2.4 g.) was chromatographed on alumina. Chloroform eluates yielded 1.0 g. of a compound, m.p. 205–206°, which was acetylated again with 10 ml. of acetic anhydride to give 1.0 g. of colorless needles, m.p. 94° (recrystallized from a mixture of benzene and petroleum ether); n.m.r. spectrum (Table I) shows that these crystals are XII. Ethanol elution yielded 0.4 g. of the product, m.p. 182–183°, which was acetylated again with 4 ml. of acetic anhydride to give 0.4 g. of colorless needles, m.p. 118° (recrystallized from a mixture of benzene and petroleum ether); n.m.r. spectrum (Table I) shows that these crystals are XIII.

5-Cyano-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (X).—A mixture of 0.6 g. of XII and 6 ml. of 5% potassium hydroxide–ethanol was allowed to stand overnight at room temperature. The solution was concentrated *in vacuo*, water was added to the residue, and the product was collected and recrystallized from ethanol to give 0.35 g. of colorless pillars, m.p. 205–206°; t.l.c., R_f 0.33; ultraviolet spectrum, λ_{max}^{EtOH} 213 mμ (log ε 3.92), 286 mμ (log ε 3.97).

Anal. Found: C, 52.21; H, 5.46; N, 30.64.

5-Cyano-3-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (XI).—A mixture of 0.4 g. of XIII and 4 ml. of 5% potassium hydroxide and 4 ml. of ethanol was allowed to stand overnight at room temperature, and concentrated *in vacuo*. Water was added to the residue and the product was recrystallized from ethanol to give 0.15 g. of colorless rhombics, m.p. 182–183°; t.l.c., R_f 0.25; ultraviolet spectrum, λ_{max}^{EtOH} 217 mμ (log ε 3.96), 278.5 mμ (log ε 3.90).

Anal. Found: C, 52.64; H, 5.37; N, 30.28.

5-Cyano-1-methyl-2-oxo-1,2-dihydropyrimidine (XIV). A.—A solution of 0.757 g. of DDQ in 10 ml. of dioxane was added to the solution of 0.457 g. of the mixture of X and XI in 10 ml. of dioxane and refluxed for 1 hr. The separated crystals were filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized from a mixture of methanol and ethyl acetate to give 0.216 g. of colorless prisms, m.p. 233–234°; the filtrate was concentrated and the residue was purified by alumina chromatography to afford 0.08 g. of the crystals. Both crystals were found to be identical by infrared spectra; t.l.c., R_f 0.15; ultraviolet spectrum, 262 mμ (log ε 4.04), 312 mμ (log ε 2.75); infrared spectrum (Nujol mull), 2255 (C≡N), 1670–1680 cm.$^{-1}$ (C=O, C=N), no NH band.

Anal. Calcd. for $C_6H_5N_3O$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.02; H, 3.91; N, 30.82.

B.—A solution of 0.137 g. of X and 0.227 g. of DDQ in 6 ml. of dioxane was refluxed for 1 hr. as described above and 0.106 g. (78.5%) of XIV was obtained.

C.—A solution of 0.044 g. of XI and 0.073 g. of DDQ in 6 ml. of dioxane was refluxed for 1 hr. as above, and 0.03 g. (69.2%) of XIV was obtained.

5-Cyano-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine (XV).—A solution of 5 g. of I, 4.8 g. of N-phenylurea, and 14 ml. of concentrated hydrochloric acid in 37 ml. of ethanol was refluxed for 5 hr. The product was collected, washed with water, and dried, yielding 4.2 g. (60%), m.p. 218–221° dec. Recrystallization from methanol gave 3.0 g. (42.6%) of colorless prisms, m.p. 220–221° dec.; ultraviolet spectrum, λ_{max}^{EtOH} 286.5 mμ (log ε 4.01).

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.56; N, 21.10. Found: C, 66.18; H, 4.74; N, 20.57.

3-Acetyl-5-cyano-2-oxo-1-phenyl-1,2,3,4-tetrahydropyrimidine (XVI).—A mixture of 0.6 g. of XV and 6 ml. of acetic anhydride was refluxed for 7 hr. After removing excess reagent, the residue was recrystallized from a mixture of benzene and petroleum ether to afford 0.7 g. (96.3%) of colorless needles, m.p. 160–163°; ultraviolet spectrum, λ_{max}^{EtOH} 283 mμ (log ε 3.99).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.43. Found: C, 64.71; H, 4.72; N, 17.04.

5-Cyano-2-oxo-2,3-dihydro-6H-1,3-thiazine (XVIII). A.—A solution of 7 g. of thiourea, 13.2 g. of I, and 35 ml. of concentrated hydrochloric acid in 700 ml. of ethanol was refluxed for 25 hr. After concentration, chloroform was added to the residue and separated ammonium chloride was filtered off. The filtrate was washed with water, dried over anhydrous magnesium sulfate, and evaporated. The residual solid was treated with charcoal and recrystallized from water to afford 4.1 g. (31.8%) of colorless pillars, m.p. 120–122°; infrared spectrum (Nujol mull), 3220 (NH), 2220 (C≡N), 1680 and 1630 cm.$^{-1}$ (amide I and conjugated C=C); ultraviolet spectrum, λ_{max}^{EtOH} 241 mμ (log ε 3.75), 285 mμ (log ε 3.74); t.l.c, R_f 0.51.

Anal. Calcd. for $C_5H_4N_2OS$: C, 42.85; H, 2.85; N, 20.00; S, 22.86. Found: C, 43.03; H, 2.98; N, 19.89; S, 23.04.

B.—A solution of 1.52 g. of thiourea, 3.8 g. of II, and 4 ml. of concentrated hydrochloric acid in 200 ml. of ethanol was refluxed for 22 hr., and treated as described above to afford 0.684 g. (24.6%) of XVIII.

5-Carboxamido-2-oxo-2,3-dihydro-6H-1,3-thiazine (XXI).—To 20 ml. of concentrated hydrochloric acid, 0.4 g. of XVIII was added and allowed to stand overnight at room temperature. Crystals were collected and recrystallized from ethanol to give 0.25 g. (55.5%) of colorless needles, m.p. 205° dec.; infrared spectrum, no C≡N band.

Anal. Calcd. for $C_5H_6N_2O_2S$: C, 37.98; H, 3.83; N, 17.72. Found; C, 38.33; H, 3.99; N, 17.79.

A mixture of 0.2 g. of XXI and 1.5 ml. of phosphorus oxychloride was refluxed for 1 hr. After evaporation of the reagent under reduced pressure, ice–water was added to the residue and the product was collected. Recrystallization from a mixture of ethyl acetate and petroleum ether gave 0.1 g. of XVIII.

3-Acetyl-5-cyano-2-oxo-2,3-dihydro-6H-1,3-thiazine (XX).—A mixture of 0.1 g. of XVIII and 2 ml. of acetic anhydride was refluxed for 6 hr. After evaporation, the residue was recrystallized from a mixture of benzene and petroleum ether to afford 0.11 g. (84.7%) of colorless needles, m.p. 107–108°; infrared spectrum, no NH band; ultraviolet spectrum, λ_{max}^{EtOH} 233 mμ (log ε 4.09).

Anal. Calcd. for $C_7H_6N_2O_2S$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.18; H, 3.55; N, 15.38.

Reaction of I with N-Phenylthiourea.—A solution of 1.4 g. of I, 1.5 g. of N-phenylthiourea, and 2 ml. of concentrated hydrochloric acid in 100 ml. of ethanol was refluxed for 12 hr. and evaporated *in vacuo*. Chloroform was added to the residue and aniline hydrochloride (0.4 g., 44.4%) was filtered off. The filtrate was evaporated and the residue was treated with charcoal, and recrystallized from water to afford 0.3 g. (21.4%) of XVIII.

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