min. When cool, the reaction mixture was decanted into 100 ml. of water, and 3.4 g. of product separated.

Compounds 1 and 6 were processed in this manner.

2-Amino-4-(β-phenethyl)amino-6-α-(4-methylpiperazino)-ethyl-s-triazine. A mixture of 2.8 g. (0.01 mole) of 2-amino-6-chloromethyl-4-β-phenethylamino-s-triazine and 6 ml. of *N*-methylpiperazine were maintained in an oil bath at 100° for 30 min. On standing 5 days the reaction mixture solidified, and after washing with water, gave 3.02 g. (89%), m.p. 140–152°; recrystallized (acetonitrile), m.p. 162–163° yielded 70% of product.

Anal. Calcd. for $C_{18}H_{27}N_7$: C, 63.3; H, 8.0; N, 28.7. Found: C, 63.2; H, 8.0; N, 28.5.

Ethyl α-pyrrolidino acetate was prepared in 63% yield from pyrrolidine and ethyl bromoacetate,[12] b.p. 58–60° (3 mm.).[13]

(12) W. V. Drake and S. M. McElvain, *J. Am. Chem. Soc.*, 56, 697 (1934).

(13) G. R. Clemo and T. A. Melrose, *J. Chem. Soc.*, 424 (1942) report b.p. 110° (27 mm.).

2-Amino-4-m-chloroanilino-6-pyrrolidinomethyl-s-triazine (Compound 4, free base, from ester and the biguanide) was prepared from the ester above, and *m*-chlorophenylbiguanide following the general procedure previously described,[1b] in 34% yield (ethyl acetate), m.p. 166–167°.

Anal. Calcd. for $C_{14}H_{17}ClN_6$: N, 27.6. Found: N, 27.3.

Its identity was confirmed by its dipicrate, m.p. 188–189° (water) which did not depress the melting point of the picrate prepared from compound 4, processed from pyrrolidine and 2-amino-4-*m*-chloroanilino-6-chloromethyl-*s*-triazine, mixed m.p. 187–188°.

Acknowledgment. The authors are indebted to Dr. G. Ungar and his staff for the pharmacological screening of the compounds and to V. Parrino for the synthesis of several compounds.

YONKERS 1, N. Y.

[CONTRIBUTION NO. 29 FROM THE L. G. RYAN RESEARCH LABORATORIES OF MONSANTO CANADA LIMITED]

Novel Condensation of Cyclohexanone with Urea

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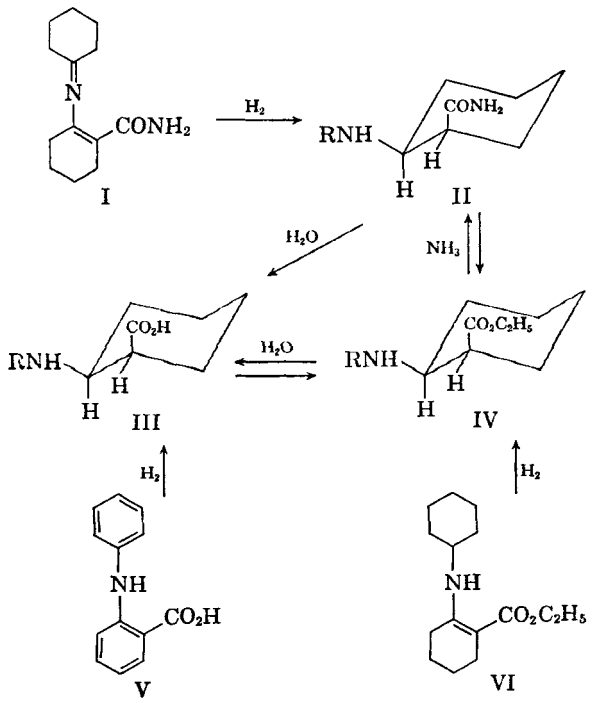
Cyclohexanone condenses with urea in an alkaline medium to give cyclohexylidene 2-carbamylcyclohex-1-enylamine. This compound on hydrogenation and acid hydrolysis gave an amino acid hydrochloride which was identical with cyclohexyl 2-carboxycyclohexylamine hydrochloride prepared from the product of the catalytic hydrogenation of *N*-phenylanthranilic acid.

Cyclohexanone condenses with urea in an alkaline medium to give an unsaturated amino acid amide which has been identified as cyclohexylidene 2-carbamylcyclohex-1-enylamine (I). The structure of this compound was verified by conversion to the saturated amino acid, cyclohexyl 2-carboxycyclohexylamine (III). The hydrochloride salt of this amino acid did not depress the melting point of a sample of cyclohexyl 2-carboxycyclohexylamine hydrochloride prepared by treating the product from the catalytic hydrogenation of *N*-phenylanthranilic acid (V) with hydrochloric acid. Since hydrogenation of *N*-phenylanthranilic acid gave a low yield (11%) of cyclohexyl 2-carboxycyclohexylamine hydrochloride, the latter acid also was prepared in 55% overall yield by the hydrogenation and hydrolysis of cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI).

Preparations of cyclohexyl 2-carbethoxycyclohexylamine (IV) from the catalytic hydrogenation of cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI) and the esterification of cyclohexyl 2-carboxycyclohexylamine (III) were found to be identical by a comparison of their physical constants and infrared spectra.

Hünig and Kahanek[1] have shown that catalytic hydrogenation of 3,4,5,6-tetrahydroanthranilic acid yields the *cis* isomer of 2-aminocyclohexanecarboxylic acid. Since the cyclohexane compounds, II, III, and IV described in this study have been prepared by the catalytic hydrogenation of unsaturated intermediates, they have been assigned the *cis*



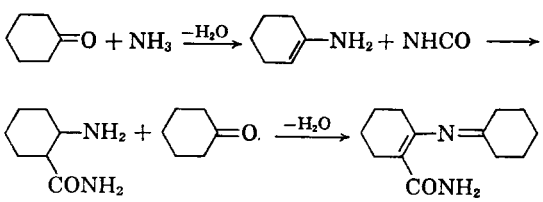
R = cyclohexyl

(1) S. Hünig and H. Kahanek, *Ber.*, 86, 518 (1953).

configuration. Also the interconversions of these compounds shown on the chart confirm the assignment of the same configuration to these three compounds. Attempts to isomerize cyclohexyl 2-carbamylcyclohexylamine hydrochloride and cyclohexyl 2-carboxycyclohexylamine hydrochloride by heating in the presence of 37% hydrochloric acid in a sealed tube at 180° lead to decomposition. This observation also agrees with the assigned *cis* configurations for these compounds. This unstable character of the *cis* compounds would be expected because the cyclohexylamine group and the hydrogen atom of the adjacent carbon atoms are trans to each other.

An attempt to prepare *trans*-cyclohexyl 2-carboxycyclohexylamine from cyclohexylamine and cyclohex-1-enecarboxylic acid by Plieninger and Schneider's[2] procedure for the preparation of *trans*-2-amino-cyclohexanecarboxylic acid was unsuccessful. A similar experiment designed to prepare *trans*-cyclohexyl 2-cyanocyclohexylamine was also unsuccessful. In both cases high yields of the starting materials were recovered.

The condensation of cyclohexanone with urea under alkaline conditions can be considered to involve an enamine intermediate. Urea splits into ammonia and isocyanic acid which can combine with cyclohexanone as follows:



This interpretation is supported to some extent by the fact that cyclohexanone condenses with ethylurea under similar conditions to give a low yield of the same product, cyclohexylidene 2-carbamylcyclohex-1-enylamine (I). Davis and Underwood[3] have demonstrated that monosubstituted ureas split in two ways as follows:

$$RNH_2 + HNCO \rightleftharpoons RNHCONH_2 \rightleftharpoons RNCO + NH_3$$

Thus ethylurea can supply the components for the formation of compound I.

In cyclohexylidene 2-carbamylcyclohex-1-enylamine, the conjugation of the amide group with the unsaturated system shifts the C=O stretching frequency from 1672 cm.$^{-1}$ (compound II) to 1625 cm.$^{-1}$ Similarly conjugation of the ester group with the double bond in cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI) shifts the absorption frequency of the ester group from 1735 (compound IV) to 1647 cm.$^{-1}$

(2) H. Plieninger and K. Schneider, *Ber.*, 92, 1594 (1959).

(3) T. L. Davis and H. W. Underwood, Jr., *J. Am. Chem. Soc.*, 44, 2595 (1922).

EXPERIMENTAL[4]

1-Cyanocyclohex-1-ene. 1-Cyanocyclohex-1-ene (b.p. 61–62°/6 mm., n_D^{25} 1.47983) was prepared in 76% yield from cyclohexanone by the method of Wheeler and Lerner.[5]

Cyclohex-1-enecarboxylic acid. 1-Cyanocyclohex-1-ene was converted into cyclohex-1-enecarboxylic acid (m.p. 36–38°) in 58% yield by the method of Wheeler and Lerner.[5]

N-(Cyclohex-1-enyl)pyrrolidine (b.p. 117–119°/19 mm) was obtained in 83% yield by the procedure of Hünig, *et al.*[6]

2-Carbethoxycyclohexanone (b.p. 117–120°/18 mm., n_D^{25} 1.47564) was prepared in 26% yield as described by Stork.[7]

Cyclohexylidene 2-carbamylcyclohex-1-enylamine (I). *Method A.* Urea (36 g., 0.6 mole), cyclohexanone (150 g., 1.53 moles) and triethanolamine (6 g.) were refluxed together for 1.5 hr. The cooled reaction mixture was dissolved in warm ethanol (100 ml.), diluted with water (200 ml.) and allowed to cool slowly. The crystals (m.p. 224–225° evac. capil.) were recovered by filtration and washed with water, yield 33.55 g. Concentration of the mother liquors gave an additional 4.1 g. of product (m.p. 215–219° evac. capil.). The total yield was 28.5%. Crystallization of the first crop from aqueous ethanol did not alter its melting point.

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.95; H, 9.16; N, 12.73. Found: C, 70.85; H, 9.11; N, 12.98.

Infrared spectrum of the solid in Nujol showed absorption bands at 3280, 3160, 1625, and 1525 cm.$^{-1}$

Method B. Ethylurea (8.8 g., 0.1 mole) and triethanolamine (1 g.) in cyclohexanone (25 g., 0.25 mole) were refluxed for 80 min. The product was separated as described above under Method A, yield 1.9 g. (8.6%). The crystals melted at 223–224° (evac. capil.) alone and on admixture with a sample of cyclohexylidene 2-carbamylcyclohex-1-enylamine prepared by Method A.

Cyclohexyl 2-carbamylcyclohexylamine (II). Cyclohexylidene 2-carbamylcyclohex-1-enylamine (5.5 g., 0.025 mole) in absolute ethanol (250 ml.) containing coned. hydrochloric acid (2.5 g., 0.025 mole) and 100 mg. of platinum oxide was hydrogenated at room temperature. Two mole equivalents of hydrogen were absorbed in about 2.5 hr. and some crystalline product separated from solution during the hydrogenation. The mixture was warmed to give a clear solution and the catalyst was removed by filtration. After the filtrate was evaporated to a small volume, crystals (m.p. 271–276°) separated, yield 5.2 g. (79.9%). Crystallization from absolute ethanol raised the melting point to a constant value of 276°.

Anal. Calcd. for $C_{13}H_{25}ClN_2O$: C, 59.86; H, 9.66; Cl, 13.59; N, 10.74. Found: C, 59.72; H, 9.82; Cl, 13.85; N, 10.37.

This hydrochloride salt (1.11 g., 0.0042 mole) was dissolved in water (25 ml.) and the *p*H was adjusted to 10 by the addition of 5% sodium hydroxide solution (4 ml.). An oil separated which crystallized within a few minutes, yield 0.79 g. (82.7%). The melting point (128°) of this free base was not changed by further crystallization.

Anal. Calcd. for $C_{13}H_{24}N_2O$: C, 69.60; H, 10.78; N, 12.49. Found: C, 69.87; H, 10.84; N, 12.06.

Cyclohexyl 2-carboxycyclohexylamine (III). Cyclohexyl 2-carbamylcyclohexylamine (1 g., 0.0045 mole) in 18% hydrochloric acid (50 ml.) was refluxed for 2 hr. The solution was evaporated to a small volume after which crystals (m.p. 249–251°) were deposited from the solution, yield 1.15 g. (98.6%). A test portion of the crystals in water gave a positive test for the chloride ion with silver nitrate solution.

(4) All melting points are uncorrected. Microanalyses were determined by Micro-Tech Laboratories, Skokie, Ill.

(5) O. H. Wheeler and I. Lerner, *J. Am. Chem. Soc.*, 78, 63 (1956).

(6) S. Hünig, E. Benzing, and E. Lucke, *Ber.*, 90, 2833 (1957).

(7) G. Stork, U. S. Patent, 2,773,099, Dec. 4 (1956).

Crystallization from methanol-dioxane solution raised the melting point to 250–251°.

Anal. Calcd. for $C_{13}H_{24}ClNO_2$: C, 59.65; H, 9.24; Cl, 13.54; N, 5.35. Found: C, 59.83; H, 9.20; Cl, 13.33; N, 5.19.

A solution of cyclohexyl 2-carbamylcyclohexylamine hydrochloride (256 mg., 0.00098 mole) in water (50 ml.) was eluted through a 7-inch column of IR 120 resin (13.5 ml.) in the hydroxyl form at a rate of 3 ml./min. The column was washed with water (100 ml.) until the eluant no longer gave a positive chloride ion test. The product was eluted from the column by washing with 10% ammonium hydroxide solution (200 ml.). The amino acid, which was obtained by evaporation of the eluant, was dissolved in ethanol and then precipitated from solution by addition of ether (100 ml.); yield 178 mg. (80.7%). The melting point was increased from 237–238° to 241–242° by recrystallizing from the same solvent pair.

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 68.77; H, 10.04; N, 6.28.

N-Phenylanthranilic acid. N-Phenylanthranilic acid (m.p. 181–184°) was prepared in 83.1% yield by the procedure of Goldberg.[8]

The crude product (25.85 g.) was dissolved in a warm solution of sodium carbonate (12.5 g.) in water (500 ml.) and treated with charcoal. After the solution had been boiled for 5 min., the charcoal was removed by filtration and the filtrate was acidified with 10% hydrochloric acid. The cooled filtrate gave 22.3 g. of product melting at 183–185°. One crystallization from ethanol-water (1:5) solution (100 ml.) raised the melting point to 186.5–187.5° (lit.[9] m.p. 182–183°), yield 17 g.

Hydrogenation of N-phenylanthranilic acid. N-Phenyl anthranilic acid (2.5 g., 0.0117 mole) in glacial acetic acid (125 ml.) was hydrogenated at 21° and 760 mm. pressure in the presence of 37% hydrochloric acid (1.10 ml., 0.018 mole) and platinum black which was obtained by reduction of platinum oxide (500 mg.) in glacial acetic acid (20 ml.). After 18 hr., 1800 ml. of hydrogen was absorbed. The calculated uptake of hydrogen for 6 moles at 21° and 760 mm. is 1689 ml.

The catalyst was removed by filtration and the filtrate was diluted with water (100 ml.), and then evaporated to dryness on the steam bath. The oily residue was dissolved in 37% hydrochloric acid and the solution was evaporated to a small volume on the steam bath under a stream of nitrogen until crystals appeared. The sludge was cooled and filtered to yield 600 mg. of crystals (m.p. 211–222°). Several crystallizations from methanol-ether (1:10) solution raised the melting point to 251–252°, yield 355 mg., 11.5%. The melting point varied from 246° to 257°. This variation in melting point is believed to be due to polymorphism. When a small amount of the compound (m.p. 251–252°) was pulverized it melted at 240–241° on the block.

Anal. Calcd. for $C_{13}H_{24}ClNO_2$: C, 59.65; H, 9.24; Cl, 13.54; N, 5.35. Found: C, 59.61; H, 9.15; Cl, 13.38; N, 5.34.

A mixed melting point determination with a sample of cyclohexyl 2-carboxycyclohexylamine hydrochloride (m.p. 251°), which was prepared by the hydrolysis of cyclohexyl 2-carbamylcyclohexylamine, showed no depression.

Cyclohexyl 2-carbethoxycyclohexylamine (IV) *from cyclohexyl 2-carbamylcyclohexylamine* (II). A solution of cyclohexyl 2-carbamylcyclohexylamine hydrochloride (16.14 g., 0.062 mole) in 37% hydrochloric acid (800 ml.) was refluxed for 2 hr. and then evaporated to dryness *in vacuo*. The white residue was dried *in vacuo* over potassium hydroxide pellets. This mixture of ammonium chloride and cyclohexyl 2-carboxycyclohexylamine hydrochloride was shaken overnight with 10% ethanolic hydrogen chloride. Most of the solid dissolved. The solution was evaporated *in vacuo* and the residue was dissolved in water. This solution was made alkaline with 5% sodium hydroxide solution and extracted with ether. The extract was washed with 5% sodium bicarbonate solution and water and then dried. After the ether was removed, the residue was fractionated in a spinning band column. The main fraction (b.p. 86°/0.1 mm., n_D^{25} 1.47786) weighed 6.72 g. (42.8%).

Anal. Calcd. for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.26; H, 10.68; N, 5.96.

Cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI). 2-Carbethoxycyclohexanone (26.2 g., 0.154 mole), cyclohexylamine (16.7 g., 0.169 mole), *p*-toluenesulfonic acid (0.35 g.), and benzene (150 ml.) were refluxed for 8 hr. The evolved water was removed by means of a Barrett trap. The solvent was removed and the residue was distilled *in vacuo* through a spinning band column. The main fraction (b.p. 116–117°/0.15 mm.; n_D^{25} 1.53057) weighed 32.5 g., (84%).

Anal. Calcd. for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.73; H, 9.66; N, 5.62.

Infrared spectrum of the solid in Nujol showed absorption bands at 3280, 3165, 1647, and 1600 cm.$^{-1}$

Hydrogenation of cyclohexyl 2-carbethoxycyclohex-1-enylamine (VI). Platinum oxide (600 mg.) in glacial acetic acid (10 ml.) was reduced to platinum black by agitation in the presence of hydrogen at atmospheric pressure. A solution of cyclohexyl 2-carbethoxycyclohex-1-enylamine (12.94 g., 0.05 mole) in acetic acid (40 ml.) was added and the hydrogenation was continued at 23° and 762 mm. pressure. Over a period of 20.5 hr. 1280 ml. of hydrogen were absorbed. The calculated uptake of hydrogenation is 1248 ml. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo* on a steam bath. The residue was then distilled. After a small amount of residual acetic acid had been removed crystals separated. The cooled mixture was diluted with ether (30 ml.) and the crystals were removed, yield 1.133 g. (9.8%). This product (m.p. 143–146°) was purified by sublimation at 80° and 0.5 mm. pressure. The sublimate (m.p. 146–147°) was identified as cyclohexylamine acetate by analysis and conversion to the known cyclohexylamine hydrochloride (m.p. 207–208°).

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found, C, 60.37; H, 10.73; N, 8.62.

The filtrate from the cyclohexylamine acetate was evaporated to dryness and the residue was fractionated in a spinning band column. The main fraction (b.p. 92°/0.1 mm., n_D^{25} 1.47769) was shown by analysis and a comparison of infrared spectra to be identical with the cyclohexyl 2-carbethoxycyclohexylamine prepared from cyclohexyl 2-carbamylcyclohexylamine. The yield was 66.2%.

Anal. Calcd. for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.22; H, 10.33; N, 5.52.

Hydrolysis of cyclohexyl 2-carbethoxycyclohexylamine in 37% hydrochloric acid gave an 83.6% yield of cyclohexyl 2-carboxycyclohexylamine hydrochloride (m.p. 239–240°). This product did not depress the melting points of samples of cyclohexyl 2-carboxycyclohexylamine hydrochloride prepared by the hydrolysis of cyclohexyl 2-carbamylcyclohexylamine and by the hydrogenation of *N*-phenylanthranilic acid.

Ammonolysis of cyclohexyl 2-carbethoxycyclohexylamine. Cyclohexyl 2-carbethoxycyclohexylamine (2.0 g., 0.0079 mole) and a catalytic amount of sodium methoxide (70 mg.) in methanol (30 ml.) saturated with ammonia was allowed to stand at room temperature for 4 weeks. Removal of the methanol gave a liquid residue which on addition of water slowly crystallized, yield 1.32 g. (74.5%), m.p. 116–120°. One recrystallization from methanol-water gave 1.00 g. (56.5%), m.p. 126–127.5°. Further recrystallization raised the melting point to a constant value of 127–128°. A mixed melting point determination with the cyclohexyl 2-carbamylcyclohexylamine (m.p. 128°) derived from the urea-cyclohexanone condensation product showed no depression.

Isomerization experiments. An attempt to isomerize cyclo-

(8) I. Goldberg, *Ber.*, **39**, 1691 (1906).

(9) C. F. H. Allen and G. H. W. McKee, *Org. Syntheses*, Coll. Vol. II, 15, (1943).

hexyl 2-carbamylcyclohexylamine hydrochloride in 37% hydrochloric acid in a sealed Carius tube at 180° for 10 hr. resulted only in complete decomposition of the product. Attempts to isomerize either cyclohexyl 2-carbamylcyclohexylamine hydrochloride or cyclohexyl 2-carboxycyclohexylamine hydrochloride in 37% hydrochloric acid at 180° for 1 hr. also resulted in decomposition. When cyclohexyl 2-carboxycyclohexylamine hydrochloride (0.5 g.) in 37% hydrochloric acid was heated at 130° for 1 hr., starting material was recovered in 64.2% yield (0.32 g., m.p. 240–241°).

Attempts to prepare trans-cyclohexyl 2-substituted cyclohexylamines (a). A mixture of 1-cyanocyclohex-1-ene (5 g., 0.046 mole), cyclohexylamine (7 g., 0.07 mole) and a few crystals of hydroquinone was sealed in a Carius tube and heated at 150° for 50 hr. The mixture on distillation *in vacuo* gave 6.19 g. (88.5%) of unchanged cyclohexylamine and 4.4 g. (88.7%) of 1-cyanocyclohex-1-ene. No other products could be identified.

(b). A solution of cyclohex-1-enecarboxylic acid (2.5 g., 0.0198 mole) and cyclohexylamine (7.85 g., 0.080 mole) in water (12.5 ml.) was heated in a Carius tube at 180° for 66 hr. The solution was evaporated to dryness and the residue was dissolved in 10% hydrochloric acid. Extraction of the acid solution with ether gave 2.4 g. (96%) of unchanged acid which was identified by a mixed melting point determination.

LaSalle, Quebec

[Contribution from the Department of Chemistry of the University of Buffalo]

Reactions of Ethoxymethylenemalononitrile with Thioureas[1]

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Ethoxymethylenemalononitrile is hydrolyzed in alkaline aqueous solvents to hydroxymethylenemalononitrile, malononitrile, or tetracyanopropene, depending on conditions. 2-Amino-3,5-dicyano-6-alkoxypyridines are formed in alkaline aqueous alcohols. 2-Amino-3,5-dicyano-6-alkylthiopyridines are formed in solutions containing mercaptans or alkylthioureas. Ethoxymethylenemalononitrile condenses with 2-alkyl-2-thiopseudoureas to give 2-alkylthio-4-amino-5-cyanopyrimidines in alkaline aqueous solvents if the nitrile is added to the thiourea.

The condensation of ethoxymethylenemalononitrile (I) with amidines, guanidine, and thioureas in anhydrous solvents to form 2-substituted-4-amino-5-cyanopyrimidines is well known.[3,4] Aqueous solvents usually are not used in these condensations although 2-methyl-4-amino-5-cyanopyrimidine has been prepared in good yield from I in an aqueous medium.[5] Because of the observations that thioureas (II) often condense well to form 2-alkylthiopyrimidines in solvents containing water, we have investigated reactions of I with thioureas in alkaline aqueous solutions.

Preliminary experiments indicated that the yields of pyrimidines in aqueous solution sometimes were low but that pyridines were also formed and that the nature of the products depended, to some extent, on the ratio of starting materials, the solvent, and the order of addition of the reagents. For example, the addition of I in acetone to a solution of 2-methyl-2-thiopseudourea (II, R = CH_3) in aqueous acetone gave a good yield of 2-methylthio-4-amino-5-cyanopyrimidine (III, R = CH_3). However, when a mixture of I and II (R = CH_3) in aqueous acetone or alcohol was brought slowly to neutrality with ammonium hydroxide, the addition of more base after one hour gave a 47% yield of 2-amino-3,5-dicyano-6-methylthiopyridine (VIII).

It was not apparent immediately that some of our products were pyridines. However, a study of the behavior of I in the presence of bases, and in the absence of thioureas was informative. When a solution of I in alcohol was added slowly to an equivalent quantity of potassium hydroxide, the potassium salt of hydroxymethylenemalononitrile (VI) was formed (80%). If a solution containing one half an equivalent of potassium hydroxide in alcohol was added slowly to I in alcohol, the salt of 1,1,3,3-tetracyanopropene (VII) was formed and an odor of ethyl formate was detected. Intermediate procedures such as the addition of potassium hydroxide in one portion to I gave mixtures of VI and VII. An excess of potassium hydroxide in water added to I in methanol gave some 2-amino-3,5-dicyano-6-methoxypyridine (XI). This latter substance was more conveniently prepared from VII, which, in turn, was prepared in quantity from anilinomethylenemalononitrile and malononitrile by the method of Strell.[6]

The above observations can be explained by considering two competing reactions of I in base through a Claisen type intermediate IV. The intermediate can lose alcohol to give VI or undergo a reverse Claisen condensation to give ethyl formate

(1) Supported by a grant CY-2857 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) In part from a thesis submitted by Steve G. Cottis to the Graduate School of Arts and Sciences, the University of Buffalo, in partial fulfillment of the requirements for the degree of Master of Arts, February 1959.

(3) R. Grewe, *Z. physiol. Chem.*, **242**, 89 (1936).

(4) W. Huber and H. A. Holsher, *Ber.*, **71B**, 87 (1938).

(5) Y. Sawa, F. Osawa, and H. Kaneko, *J. Pharm. Soc. Japan*, **67**, 204 (1947); *Chem. Abstr.*, **45**, 9063 (1951).

(6) M. Strell, W. B. Braunbuck, W. F. Fuhler, and O. Huber, *Ann.*, **587**, 177 (1954).