2-Selenothymine.—A solution of 2.0 g. of crude sodium ethylformyl propionate,[9] 1.62 g. (0.0132 mole) of selenourea and 0.43 g. of sodium in 30 cc. of absolute ethanol was heated to reflux for 3 hours. The solution was evaporated to dryness under aspirator suction. The dark red residue dissolved easily in 8 cc. of water. The solution was filtered and the filtrate acidified with acetic acid. After refrigeration 0.8 g. of purple solid separated, only part of which dissolved when treated with 15 cc. of boiling ethanol. Chilling the ethanol solution resulted in the separation of 0.1 g. of coarse, pale yellow needles which melted at 228.5–229.5°.

Anal. Calcd. for $C_5H_6ON_2Se$: C, 31.76; H, 3.20; N, 14.82. Found: C, 32.08; H, 3.31; N, 14.60.

2,4-Dithiouracil.—A modification[15] of the method of Wheeler and Liddle[8] was used. A solution of 1.6 g. of sodium shavings in 70 cc. of absolute ethanol was saturated with hydrogen sulfide. Then 2.5 g. (0.0169 mole) of 2,4-dichloropyrimidine was added and the mixture was permitted to reflux for 5 hours. Acidification yielded 1.2 g. (48%) of the desired product which was recrystallized from boiling water.

2-Thiouracil, 2-Thiothymine.—The syntheses of Wheeler and Liddle[8] and of Wheeler and McFarland[9] were utilized. The products were purified by recrystallization from absolute ethanol.

Ultraviolet Spectra.—A Beckman model DU spectrophotometer with quartz cells was utilized for all measurements. Solutions were made up in volumetric flasks from weighed quantities of the compounds.

Dissociation Constants.—The pK_a's were determined potentiometrically using a Beckman model G or a Cambridge *p*H meter. In 100 cc. of carbon dioxide-free water dissolved 0.0005-mole samples of the compounds investigated. They were then titrated with 0.050 *N* sodium hydroxide. To 2,4-dithiouracil and 2,4-diselenouracil, which are extremely insoluble in water, equimolar quantities of 0.050 *N* sodium hydroxide were added and the solutions back-titrated with 0.050 *N* hydrochloric acid. All determinations were made in duplicate.

NEW HAVEN, CONN.

(15) Analogous to S. B. Greenbaum and W. L. Holmes, THIS JOURNAL, **76**, 2899 (1954).

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

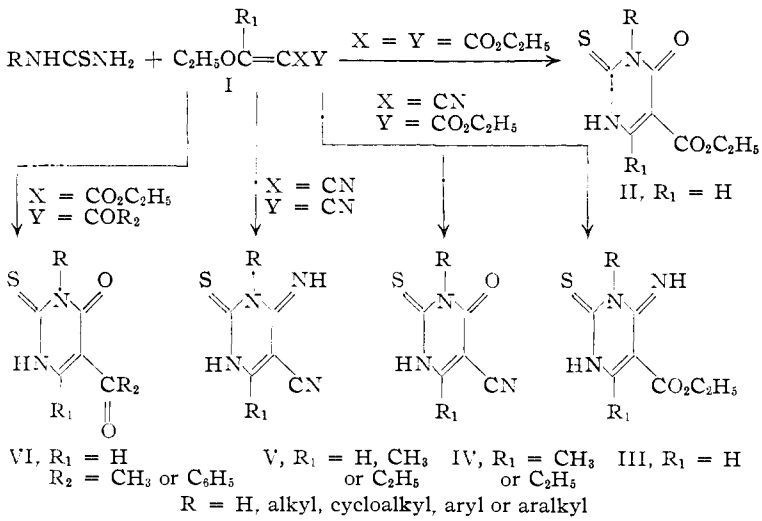
Synthesis of 2-Thiocytosines and 2-Thiouracils

BY CALVERT W. WHITEHEAD AND JOHN J. TRAVERSO

RECEIVED APRIL 30, 1956

Forty-six new 2-thiouracils and 2-thiocytosines were prepared by the condensations of thioureas with ethoxymethylene derivatives of diethyl malonate, ethyl cyanoacetate, ethyl benzoylacetate, ethyl acetoacetate and malononitrile. These thiopyrimidines were then converted by known procedures to other new pyrimidines.

In previous papers[1-3] the reactions of ureas with ethoxymethylene derivatives of diethyl malonate, ethyl cyanoacetate and ethyl oxalacetate were shown to yield carbethoxypyrimidines. In this present work, ethoxymethylene derivatives of this general type were allowed to react with thioureas to yield 5-cyano-, 5-keto- and 5-carbethoxy-2-thiouracils and thiocytosines. These pyrimidines were prepared for evaluation as anticancer and antiviral agents.



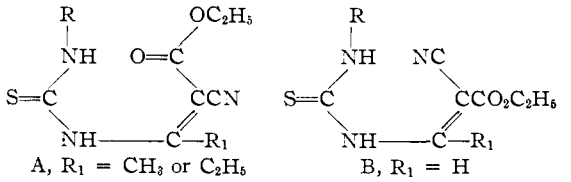
Diethyl ethoxymethylenemalonate reacted with N-alkyl- and N-arylthioureas to give excellent yields of 5-carbethoxy-2-thiouracils (II). Equally good yields of 5-carbethoxy-2-thiocytosines (III) and 5-cyano-2-thiocytosines (V) were obtained from the above thioureas with ethyl ethoxymethylenecyanoacetate and ethoxymethylenemalononitrile, respectively. The 5-cyano-6-methyl-2-thiocytosines (V, R_1 = CH_3) were obtained from 1-ethoxyethylidinemalononitrile and the 5-cyano-6-ethyl-2-thiocytosines (V, R_1 = C_2H_5) from 1-ethoxypropylidinemalononitrile. Condensations of thioureas with ethoxymethyleneacetoacetate yielded 5-acyl-2-thiouracils (VI, R_2 = CH_3) and with ethyl ethoxymethylenebenzoylacetate yielded 5-benzoyl-2-thiouracils (VI, R_2 = C_6H_5). Reactions of these ethoxymethylene derivatives were found generally applicable to all the thioureas tried. Thus, preparation of thiopyrimidines having desired functional groups in the 5-position was particularly convenient. The ethoxymethylene derivatives used in these condensations were prepared by known reactions of orthoesters with appropriate active methylene compounds.

The reactions with unsymmetrical N-alkyl- and N-arylthioureas could supposedly yield 2-thiopyrimidines with the alkyl or aryl groups in either the 1-position or the 3-position on the ring. The structure of representative 2-thiouracils and 2-thiocytosines and the position of substituent groups were

(1) C. W. Whitehead, THIS JOURNAL, **74**, 4267 (1952).
(2) C. W. Whitehead, *ibid.*, **77**, 5867 (1955).
(3) R. G. Jones and C. W. Whitehead, *J. Org. Chem.*, **20**, 1342 (1955).

therefore unambiguously established by their conversion to known pyrimidines. Thus, 5-carbethoxy-3-*n*-octyl-2-thiouracil was hydrolyzed, under mild conditions, with concentrated nitric acid to yield the previously described 5-carbethoxy-3-*n*-octyluracil.[1] Hydrolysis of 5-carbethoxy-3-phenyl-2-thiouracil with dilute nitric acid[4] yielded the known 3-phenyl-5-carboxyuracil.[1] It was also possible to desulfurize 2-thiocytosines by nitric acid hydrolysis to obtain cytosines, and 5-carbethoxy-3-methyl-2-thiocytosine was converted to the known 5-carbethoxy-3-methylcytosine.[2,5] Reactions of the thiopyrimidines with nitric acid were of some added interest in that the sulfur was removed by hydrolysis and under controlled conditions either 5-carbethoxy or 5-carboxypyrimidines could be obtained as desired. Another hydrolytic desulfurization of 2-methylmercaptopyrimidines, using hydrochloric acid, has been described by Wheeler and Jamieson.[6] This method was employed in converting the S-methyl derivative of 5-carbethoxy-3-methyl-2-thiouracil to 5-carboxy-3-methyluracil which then decarboxylated to yield the well-known 3-methyluracil. Ultraviolet and infrared spectra of the compounds described in this paper were consistent with the assigned structures and gave no indication that more than one isomer was formed during any one reaction. A study of the physical properties of these compounds will be published later.

The condensation of thiourea and ethyl ethoxymethylenecyanoacetate was recently reported by Ulbricht and Price[7] to yield two products. 5-Carbethoxy-2-thiocytosine was obtained as the major component and 5-cyano-2-thiouracil as a minor component. In the reactions reported here of ethyl ethoxymethylenecyanoacetate with thiourea and N-substituted thioureas, only 5-carbethoxy-2-thiocytosines were isolated. However, when ethyl 1-ethoxyethylidinecyanoacetate and ethyl 1-ethoxypropylidinecyanoacetate were allowed to react with thioureas, the products were not 5-carbethoxy-2-thiocytosines but were 5-cyano-2-thiouracils (IV). This striking and complete change in the course of the cyclization was obviously due to the alkyl substituent (R_1) on the β-carbon of I. A possible reason is seen for the formation of uracils, rather than cytosines, when the intermediates in these reactions are considered. Intermediates in reactions of this type were shown[1] to be ureidomethylenecyanoacetates for which two structures A and B may be written. It is suggested by reason of steric factors that structure A is more stable thermodynamically than B when R_1 is CH_3 or C_2H_5 and that isomer B is more stable than A when R_1 is H. The alkyl group R_1 in structure A is larger than the NH group, and the $CO_2C_2H_5$ group is in turn larger than the linear CN group. Structure A with these larger groups in a *trans* position is therefore more stable than a structure would be with these groups in a *cis* position. In structure B, the NH group has greater effective bulk than R_1, since the latter is H, and the more stable configuration is then as shown with NH and $CO_2C_2H_5$ in a *trans* position. It is apparent from Stuart–Briegleb molecular models that structure A can cyclize only one way and that is to yield the 5-cyano-2-thiouracil. Similarly, structure B is oriented so that only the cyano group can take part in the cyclization to yield 5-carbethoxy-2-thiocytosines. Isomerization about the carbon–carbon double bond is required before A can be converted to B. This isomerization was attempted by ultraviolet irradiation under conditions known to cause isomerization of conjugated double bond systems.[8] This, however, failed and the product was again the 5-cyano-2-thiouracil. It is suggested here without proof that reactions of thioureas with ethoxymethylenecyanoacetate yield predominantly thioureidomethylenecyanoacetates with configuration B. Ethyl 1-ethoxyethylidinecyanoacetate and ethyl 1-ethoxypropylidinecyanoacetate yield thioureidomethylenecyanoacetates with structure A. These configurations then determine whether the cyclized product is a cytosine or a uracil. This argument does not preclude the possibility that configurations A and B may be predetermined by *cis* or *trans* forms of the ethoxymethylene and ethoxyalkylidinecyanoacetates.



Saponification and simultaneous desulfurization of 5-carbethoxythiocytosine (III, R = H) with Raney nickel yielded 4-amino-5-carboxypyrimidine. In the course of physical investigation of this compound, the spectral data led us to examine its ionic character. Titration in water gave one group with pK'_a 5.60 and the other with a pK'_a less than 2.0. In 66% N,N-dimethylformamide, the pK'_a's were found to be 2.8 ± 0.2 and 5.60. The coincidence of the upper pK'_a in water and in 66% N,N-dimethylformamide is unlike the behavior of either anthranilic acid, which is a non-zwitterion, or of β-alanine, a zwitterion. The carboxy group of anthranilic acid shifts from pK'_a 4.95 in water to pK'_a 7.45 in 66% N,N-dimethylformamide. The amino group of β-alanine shows an increase in pK'_a from 10.30 in water to 10.67 in 66% N,N-dimethylformamide. The above pK'_a values and the ultraviolet data (Table III) establish a zwitterion character for 4-amino-5-carboxypyrimidine in water, but show less charge separation in 66% N,N-dimethylformamide. The ultraviolet data also show little, if any, charge separation in methanol. The compound was therefore further examined to determine its form in other proportions of N,N-dimethylformamide and water. When a water solution of 4-amino-5-carboxypyrimi-

(4) R. Robinson and M. L. Tomlinson, *J. Chem. Soc.*, **138**, 1284 (1935).

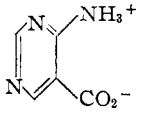
(5) 5-Carbethoxy-3-methylcytosine was previously reported[2] to yield 3-methylcytosine upon saponification and decarboxylation. It has now been proved by D. J. Brown (*J. Applied Chem.*, **5**, 363 (1955)) that this assumed 3-methylcytosine was actually 2-hydroxy-4-methylaminopyrimidine. An interesting rearrangement occurred during decarboxylation involving a shift of the methyl group from the nuclear nitrogen to the extranuclear nitrogen.

(6) H. L. Wheeler and J. S. Jamieson, *Am. Chem. J.*, **32**, 349 (1904).

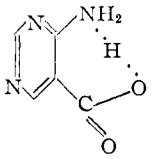
(7) T. L. V. Ulbricht and C. C. Price, *Chemistry and Industry*, **39**, 1221 (1955); also by personal communication.

(8) G. M. Wyman, *Chem. Revs.*, **55**, 625 (1955).

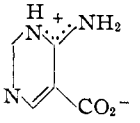
dine was titrated first with alkali to *p*H 5.60 and then with N,N-dimethylformamide, the pK'_a showed a minimum of 5.20 in 40% dimethylformamide and rose to 6.35 in 78% dimethylformamide. These observations demonstrate the gradual decrease in its charge separation with decreasing dielectric constant. Alkali titration of 4-amino-5-carboxypyrimidine, in the lower dielectric constant solvents, is not simply removal of a proton from the carboxy group or from the amino group, but is very likely the withdrawal of a proton shared by both groups. The infrared data (Table IV) of 4-amino-5-carboxypyrimidine show the solid to have zwitterionic character with carboxylate and aminidinium-like ions. The position and breadth of bands also show strong electronic and hydrogen interaction between molecules. The ionic character of 4-amino-5-carboxypyrimidine is represented graphically by



in water



in methanol and in 66% N,N-dimethylformamide



in solid state

There seemed to be a difference between 5-keto-2-thiouracils and 5-carbethoxy-2-thiouracils in their ease of methylation. The 5-keto-2-thiouracils yielded S-methyl derivatives when treated with methyl iodide in aqueous base. Under these same conditions, the 5-carbethoxy-2-thiouracils were unchanged. When dimethyl sulfate was employed, however, the 5-carbethoxy-2-methyl-thio-4(3H)-pyrimidinone was obtained.

Acknowledgment.—The authors thank W. L. Brown, H. L. Hunter, G. M. Maciak and G. Beckmann for the microanalyses reported here. We are also grateful to Martha Hofmann, James W. Forbes and Dr. Harold Boaz for the physical data and their interpretation.

Experimental

1-Ethoxypropylidinemalononitrile.—A mixture of 152.2 g. (1 mole) of triethyl orthopropionate and 66 g. (1 mole) of malononitrile was heated under reflux for 5 hours. The mixture was fractionated through a Vigreux column fitted with a partial take-off head. The fraction boiling at 142° and 7.0 mm. was collected; yield 109 g. (73%), $n^{25}D$ 1.4871.

Anal. Calcd. for $C_8H_{10}N_2O$: N, 18.65. Found: N, 18.91.

Ethyl 1-Ethoxypropylidinecyanoacetate.—A mixture of 152.2 g. (1 mole) of triethyl orthopropionate and 113 g. (1 mole) of ethyl cyanoacetate was heated under reflux for 5 hours. The mixture was concentrated at 10 mm. on the steam-bath. The remaining oil was fractionated through an 18-inch Vigreux column to yield 60 g. of ethyl cyanoacetate, b.p. 94° at 9 mm., and 60 g. (30%) of ethyl 1-ethoxypropylidinecyanoacetate, b.p. 158° at 9 mm. The latter crystallized and was recrystallized from petroleum ether, m.p. 62°.

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 61.35; H, 7.91; N, 7.40.

3-Alkyl- and 3-Aryl-5-carbethoxy-2-thiouracils (Table I).—Four and six-tenths grams (0.2 g. atom) of sodium was added to 300–400 ml. of absolute ethanol. After the sodium had reacted, 0.2 mole of the appropriate N-alkyl- or N-arylthiourea was added with 43.2 g. (0.2 mole) of diethyl ethoxymethylenemalonate.[9] The solution was allowed to stand at room temperature for 3 to 5 days. The alcohol was evaporated, under reduced pressure, to a volume of 100–150 ml. Cold water was added to make a volume of 400–500 ml. The resulting solution was made weakly acidic with 6 *N* HCl. The 5-carbethoxy-2-thiouracil separated and crystallized. The solid was collected by filtration, washed with water and dried. The 5-carbethoxy-2-thiouracils obtained by this procedure were recrystallized from ethyl alcohol.

3-Alkyl- and 3-Aryl-5-carbethoxy-2-thiocytosines (Table II).—Four and six-tenths grams (0.2 g. atom) of sodium metal was allowed to react with 400 ml. of absolute ethanol, under reflux. When this reaction was completed, 0.2 mole of the appropriate N-alkyl- or N-arylthiourea and 33.8 g. (0.2 mole) of ethyl ethoxymethylenecyanoacetate[10] was added. The resulting solution was allowed to stand in the stoppered flask for five days. The alcohol was concentrated to 200 ml. under reduced pressure. An equal volume of cold water was added and the resulting solution was made acidic with glacial acetic acid. The solid 5-carbethoxy-2-thiocytosine was collected and recrystallized from ethyl alcohol or a mixture of ethyl alcohol and N,N-dimethylformamide.

3-Alkyl- and 3-Aryl-5-cyano-2-thiocytosines (Table II).—To a solution of 10.8 g. (0.2 mole) of sodium methoxide in 400 ml. of methanol was added 0.2 mole of the appropriate thiourea and 24.4 g. (0.2 mole) of ethoxymethylenemalononitrile.[11] The solution was allowed to stand for 2 to 3 days and then concentrated to a volume of 150 ml. Cold water was added to make a volume of 500 ml. and this was then acidified with glacial acetic acid. The 5-cyano-2-thiocytosine crystallized and was purified by recrystallization from ethyl alcohol.

Nitric Acid Desulfurization of 5-Carbethoxy-2-thiouracils. 3-*n*-Octyl-5-carbethoxyuracil.—Ten grams of 5-carbethoxy-3-*n*-octyl-2-thiouracil was dissolved in 40 ml. of glacial acetic acid by warming the mixture on the steam-bath. This solution was cooled in tap water (15°), and concentrated nitric acid was added a drop at a time. A vigorous reaction occurred with evolution of red fumes of nitrogen oxides. The reaction was allowed to subside after addition of each drop of nitric acid. The temperature was maintained at approximately 15° by the cold water-bath. Addition of the nitric acid was continued until evolution of the red fumes was complete. The solution was removed from the water-bath and the reaction again proceeded vigorously for 5–10 minutes. An equal volume of cold water was added and white crystalline product separated. Cold water was then added until the separation was complete. The solid was collected, dried and recrystallized from ethyl acetate; yield 5 g. (55%), m.p. 130°. This product was found to be identical with a known sample of 5-carbethoxy-3-*n*-octyluracil.[1]

5-Carboxy-3-phenyluracil.—Small portions (0.2–0.5 g.) of 5-carbethoxy-3-phenyl-2-thiouracil were added to 60 ml. of 7.5 *N* nitric acid. After the first small addition, 0.1 g. of sodium nitrite was added and the mixture warmed slightly until evolution of red fumes started. It was then cooled to room temperature and addition of the thiouracil continued at such a rate that the temperature did not exceed 30–35°. After the addition of 10 g. of 5-carbethoxy-3-phenyl-2-thiouracil and after the bubbling had ceased (0.5 hour), cold water was added to precipitate the product. The solid was collected, dried and recrystallized from ethyl acetate; yield 5 g. (59%), m.p. 243° dec.[1]

5-Carbethoxy-3-methyl-2-methylthio-4(3H)-pyrimidinone and 5-Carboxy-3-methyl-2-methylthio-4(3H)-pyrimidinone.—Four grams of sodium hydroxide was dissolved in 200 ml. of water. To this was added 21.4 g. (0.1 mole) of 5-carbethoxy-3-methyl-2-thiouracil. The solution was stirred mechanically and 12.6 g. (0.1 mole) of dimethyl sulfate was

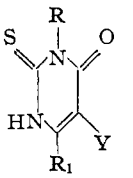
(9) Obtained from Kay–Fries Chemicals, Inc., 180 Madison Avenue, New York, N. Y.

(10) C. C. Price, N. J. Leonard and H. F. Herbrandson, THIS JOURNAL, **68**, 1252 (1946).

(11) O. Diels, H. Gartner and R. Kaack, *Ber.*, **55**B, 3441 (1922).

TABLE I

2-THIOURACILS

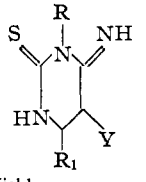


R	R_1	Y	Formula	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	H	$CO_2C_2H_5$	$C_8H_{10}N_2O_3S$	79	205 d.	44.86	44.90	4.71	4.74
C_2H_5	H	$CO_2C_2H_5$	$C_9H_{12}N_2O_3S$	72	257	47.37	47.32	5.30	5.41
$H_2C{=}CHCH_2$	H	$CO_2C_2H_5$	$C_{10}H_{12}N_2O_3S$	78	221	50.00	50.01	5.04	5.07
n-C_3H_7	H	$CO_2C_2H_5$	$C_{10}H_{14}N_2O_3S$	75	212	49.58	49.50	5.83	6.04
$CH_3O(CH_2)_2$	H	$CO_2C_2H_5$	$C_{10}H_{14}N_2O_4S$	95	202	46.51	46.46	5.47	5.48
n-C_4H_9	H	$CO_2C_2H_5$	$C_{11}H_{16}N_2O_3S$	72	192	51.56	51.75	6.29	6.23
iso-C_4H_9	H	$CO_2C_2H_5$	$C_{11}H_{16}N_2O_3S$	68	189	10.93[a]	10.84[a]	12.51[b]	12.31[b]
n-C_5H_{11}	H	$CO_2C_2H_5$	$C_{12}H_{18}N_2O_3S$	78	196	53.32	53.04	6.71	6.97
iso-C_5H_{11}	H	$CO_2C_2H_5$	$C_{12}H_{18}N_2O_3S$	70	184	53.32	53.40	6.71	6.99
C_6H_5	H	$CO_2C_2H_5$	$C_{13}H_{12}N_2O_3S$	83	276 d.	56.50	56.14	4.38	4.62
C_6H_{11}	H	$CO_2C_2H_5$	$C_{13}H_{18}N_2O_3S$	90	194	55.31	55.53	6.43	6.73
n-C_6H_{13}	H	$CO_2C_2H_5$	$C_{13}H_{20}N_2O_3S$	69	196	55.00	54.66	7.08	7.21
$C_6H_5CH_2$	H	$CO_2C_2H_5$	$C_{14}H_{14}N_2O_3S$	95	228	57.93	57.59	4.86	4.67
n-C_8H_{17}	H	$CO_2C_2H_5$	$C_{15}H_{24}N_2O_3S$	74	170	57.65	57.35	7.71	7.64
CH_3	CH_3	CN	$C_7H_7N_3OS$	53	280 d.	46.41	46.59	3.90	4.12
$CH_3O(CH_2)_2$	CH_3	CN	$C_9H_{11}N_3O_2S$	78	207	48.00	47.73	4.92	4.60
n-C_4H_9	CH_3	CN	$C_{10}H_{13}N_3OS$	46	234	53.80	54.16	5.87	6.06
iso-C_3H_7	H	CH_3CO	$C_9H_{12}N_2O_2S$	64	144	50.94	51.18	5.70	5.72
$CH_3O(CH_2)_2$	H	CH_3CO	$C_9H_{12}N_2O_3S$	75	137	47.37	47.76	5.30	5.28
C_6H_5	H	CH_3CO	$C_{12}H_{10}N_2O_2S$	95	232	58.53	58.57	4.09	4.31
C_6H_{11}	H	CH_3CO	$C_{12}H_{16}N_2O_2S$	94	198	57.13	57.23	6.39	6.28
C_2H_5	H	C_6H_5CO	$C_{13}H_{12}N_2O_2S$	80	253	59.99	60.05	4.65	4.67
n-C_4H_9	H	C_6H_5CO	$C_{15}H_{16}N_2O_2S$	84	183	62.49	62.50	5.59	5.69

[a] Nitrogen values. [b] Sulfur values.

TABLE II

2-THIOCYTOSINES



R	R_1	Y	Formula	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	H	$CO_2C_2H_5$	$C_8H_{11}N_3O_2S$	70	238 d.	45.07	45.01	5.20	5.18
C_2H_5	H	$CO_2C_2H_5$	$C_9H_{13}N_3O_2S$	98	252	47.57	47.30	5.76	5.41
$CH_3O(CH_2)_2$	H	$CO_2C_2H_5$	$C_{10}H_{15}N_3O_3S$	72	206	46.69	46.54	5.88	5.89
n-C_4H_9	H	$CO_2C_2H_5$	$C_{11}H_{17}N_3O_2S$	64	249	51.75	52.06	6.71	6.61
iso-C_4H_9	H	$CO_2C_2H_5$	$C_{11}H_{17}N_3O_2S$	92	235	51.75	51.70	6.71	6.78
n-C_5H_{11}	H	$CO_2C_2H_5$	$C_{12}H_{19}N_3O_2S$	75	228	53.52	53.56	7.11	7.29
iso-C_5H_{11}	H	$CO_2C_2H_5$	$C_{12}H_{19}N_3O_2S$	80	252	53.52	53.20	7.11	7.11
C_6H_5	H	$CO_2C_2H_5$	$C_{13}H_{13}N_3O_2S$	65	251	56.72	56.48	4.76	4.78
C_6H_{11}	H	$CO_2C_2H_5$	$C_{13}H_{19}N_3O_2S$	80	>250	55.50	55.53	6.81	6.72
n-C_6H_{13}	H	$CO_2C_2H_5$	$C_{13}H_{21}N_3O_2S$	80	240	55.11	55.14	7.47	7.35
$C_6H_5CH_2$	H	$CO_2C_2H_5$	$C_{14}H_{15}N_3O_2S$	90	241	58.12	58.24	5.23	5.31
n-C_8H_{17}	H	$CO_2C_2H_5$	$C_{15}H_{25}N_3O_2S$	93	243	57.86	58.28	8.09	8.43
iso-C_3H_7	H	CN	$C_8H_{10}N_4S$	90	178	49.48	50.20	5.19	5.42
$CH_3O(CH_2)_2$	H	CN	$C_8H_{10}N_4OS$	60	198	45.71	45.93	4.80	4.75
n-C_4H_9	H	CN	$C_9H_{12}N_4S$	95	228	51.91	51.72	5.81	5.91
C_6H_5	H	CN	$C_{11}H_8N_4S$	73	242	57.89	57.99	3.53	3.60
n-C_8H_{17}	H	CN	$C_{13}H_{20}N_4S$	95	225	59.07	59.21	7.63	7.84
$CH_3O(CH_2)_2$	CH_3	CN	$C_9H_{12}N_4OS$	65	233	48.21	48.43	5.39	5.47
n-C_4H_9	CH_3	CN	$C_{10}H_{14}N_4S$	54	256	54.04	54.26	6.35	6.30
$CH_3O(CH_2)_2$	C_2H_5	CN	$C_{10}H_{14}N_4OS$	75	202	50.42	50.72	5.92	6.22
iso-C_3H_7	C_2H_5	CN	$C_{10}H_{14}N_4S$	79	254	54.04	54.27	6.35	6.46
C_6H_{11}	CH_3	CN	$C_{12}H_{16}N_4S$	85	>270	58.05	58.24	6.50	6.88
n-C_8H_{17}	C_2H_5	CN	$C_{15}H_{24}N_4S$	60	245	61.62	61.60	8.27	8.24

added dropwise. The reaction mixture became warm (40–50°) and a solid crystallized from solution. The mixture was cooled in an ice-bath and the crystalline 5-carbethoxy-3-methyl-2-methylthio-4(3H)-pyrimidinone was collected. This was recrystallized from a mixture of ethyl acetate and petroleum ether; yield 5 g. (22%), m.p. 153°.

Anal. Calcd. for $C_9H_{12}N_2O_3S$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.54; H, 5.45; N, 12.05.

The alkaline filtrate obtained above was acidified with acetic acid to yield 5-carboxy-3-methyl-2-methylthio-4(3H)-pyrimidinone. This was added to 30 ml. of dilute $NaHCO_3$ solution, filtered and acidified with acetic acid. The solid that separated was collected and recrystallized from ethanol; yield 4 g. (20%), m.p. 205–212° dec.

Anal. Calcd. for $C_7H_8N_2O_3S$: C, 42.00; H, 4.03; N, 14.00. Found: C, 42.41; H, 3.95; N, 14.07.

To 45 ml. of 3 *N* HCl was added 2.5 g. of 5-carbethoxy-3-methyl-2-methylthio-4(3H)-pyrimidinone. The solution was heated under reflux for 12 hours. The resulting clear solution was cooled to obtain 1 g. (45%) of 5-carboxy-3-methyl-2-methylthio-4(3H)-pyrimidinone, m.p. 205–212° dec.

3-Methyluracil from 5-Carbethoxy-3-methyl-2-methylthio-4(3H)-pyrimidinone.—To 40 ml. of 12 *N* HCl was added 1.5 g. of 5-carbethoxy-3-methyl-2-methylthio-4(3H)-pyrimidinone. The mixture was heated under reflux. The solid dissolved and after 1–2 hours 5-carboxy-3-methyl-2-methylthio-4-(3H)-pyrimidinone crystallized from solution. The heating was continued and the crystals dissolved. The solution was cooled after 6 hours. The product separated and was recrystallized from ethanol to yield 0.5 g. (66%) of 3-methyluracil, m.p. 174–176°.[1]

3-Alkyl-5-cyano-6-methyl-2-thiouracils (Table I).—To a solution of 0.2 mole of sodium ethylate in 300 ml. of absolute ethanol was added 0.2 mole of the appropriate N-alkylthiourea and 36.6 g. (0.2 mole) of ethyl 1-ethoxyethylidinecyanoacetate.[12] The solution was allowed to stand in a stoppered flask for five days. The alcohol solution was concentrated and diluted with water. The 3-alkyl-5-cyano-6-methyl-2-thiouracil crystallized when the aqueous solution was acidified with dilute hydrochloric acid. It was then recrystallized from a mixture of 80% ethanol and 20% N,N-dimethylformamide.

5-Cyano-6-ethyl-3-phenyl-2-thiouracil.—To a solution of 0.1 mole of sodium ethylate in 400 ml. of absolute ethanol was added 15.2 g. (0.1 mole) of phenylthiourea and 29.7 g. (0.1 mole) of ethyl 1-ethoxypropylidinecyanoacetate. The resulting solution was allowed to stand at room temperature for 5 days. An equal volume of water was added and the solution was then acidified with glacial acetic acid. The precipitated solid was recrystallized from ethanol, in which it is only slightly soluble (5 g. in 300–400 ml.); m.p. 263° dec., yield 18 g. (45%).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.75; H, 4.43; N, 16.58.

Attempted Inversion of the Reaction between Ethyl 1-Ethoxyethylidinecyanoacetate and N-Ethylthiourea.—A solution of 18.3 g. (0.1 mole) of ethyl 1-ethoxyethylidinecyanoacetate and 150 ml. of absolute ethanol was irradiated with light of a wave length of 365 Å. After 12 hours of irradiation 10.4 g. (0.1 mole) of N-ethylthiourea was added and the irradiation continued for another 12 hours. A solution of 0.1 mole of sodium ethylate in 100 ml. of ethanol was added and the irradiation continued for 8 hours. The alcohol solution was then concentrated to 100 ml. and diluted with an equal volume of cold water. This was acidified with acetic acid. The resulting solid was recrystallized to yield 10.5 g. (54%) of 5-cyano-3-ethyl-6-methyl-2-thiouracil, m.p. 268°. The irradiation had not affected a change in the course of the reaction.

Anal. Calcd. for $C_8H_9N_3OS$: C, 49.23; H, 4.65. Found: C, 49.15; H, 4.74.

5-Carbethoxythiocytosine.—One hundred and fifty-two grams (2 moles) of thiourea and 338 g. (2 moles) of ethyl ethoxymethylenecyanoacetate were added to 2.5 liters of absolute ethanol containing 136 g. (2 moles) of sodium ethylate. After the warm mixture was allowed to stand for several days, the ethanol was removed under reduced pressure. The yellow sodium salt was dissolved in 4 liters of water, decolorized with carbon and filtered. The solution was acidified with acetic acid and cooled. The 5-carbethoxy-2-thiocytosine was filtered off and dried; yield 221 g. (55%). This was recrystallized from ethanol, m.p. 273°.

Anal. Calcd. for $C_7H_9N_3O_2S$: C, 42.20; H, 4.55. Found: C, 42.28; H, 4.26.

4-Amino-5-carboxypyrimidine.—Eighty grams (0.4 mole) of 5-carbethoxy-2-thiocytosine was dissolved in 1.5 liters of water containing 16 g. (0.4 mole) of sodium hydroxide. To the stirred solution in a 3-liter 3-necked flask was added, portionwise, 200 g. (wet weight) of Raney nickel. The mixture was refluxed with stirring for 4 or 5 hours. The hot mixture was filtered, decolorized with carbon and filtered again. The filtrate was acidified with acetic acid and concentrated, under reduced pressure, to one-third the original volume. The 4-amino-5-carboxypyrimidine was filtered from the cooled solution and dried; yield 26 g. (47%). This was precipitated from 1 *N* sodium hydroxide with 1 *N* HCl, m.p. 270° dec.

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.17; H, 3.62; N, 30.21. Found: C, 43.33; H, 3.73; N, 29.92.

Spectral Data for 4-Amino-5-carboxypyrimidine.—Ultraviolet absorption of 4-amino-5-carboxypyrimidine was determined on the Cary model II spectrophotometer. The results are summarized in Table III.

TABLE III

ULTRAVIOLET DATA FROM 4-AMINO-5-CARBOXYPYRIMIDINE

Solvent	pH	λ_1 mμ	log ϵ_1	λ_2 mμ	log ϵ_2
Water	1.3	246	4.10	283	3.52[a]
	4.0	248	4.08	281	3.51[a]
	9.6	240	4.06	293	3.61
66% DMF[b]	2.5	250		287	3.48[a]
	4.5	≤245		291	3.48[a]
	9.0	≤242		293	3.59
Methanol	0.03 *M* H^+	247	4.10	282	3.58
Methanol		241	4.01	294	3.51
	.03 *M* OH^-	240	4.00	292	3.54
Mineral oil[c]		265		305	

[a] Graphically resolved. [b] N,N-Dimethylformamide, useful above 242 mμ in 0.10-mm. path. [c] A very finely ground suspension of the crystalline compound in mineral oil.

The infrared data for 4-amino-5-carboxypyrimidine and its hydrochloride were obtained in mineral oil by the Beckman IR-2T spectrophotometer equipped with sodium chloride optics. The results are summarized in Table IV.

TABLE IV

INFRARED DATA FROM 4-AMINO-5-CARBOXYPYRIMIDINE AND ITS HYDROCHLORIDE

Mineral oil mull of	λμ	Assignment
Zwitterion form	3.1, 3.2	Weakly hydrogen bonded NH or NH_2
	4.2,[a] 4.8,[a] 5.2[a]	Strongly bonded hydrogen
	6.1,[b] 6.6[a]	Amidinium-like ion
	6.33, 7.5[c]	Carboxylate ion (CO_2^-)
Acid salt	3.05[c]	–NH
	3 to 4[a]	$-NH^+$ and carboxyl
	5.90	Carboxyl (CO_2H)
	6.1,[b] 6.6, 6.5	Amidinium-like ion

[a] Broad band. [b] Double band. [c] Narrow band.

5-Cyano-3,6-dialkyl-2-thiocytosines (Table II).—One-half mole of sodium methylate (27 g.) was added to 1 liter of methanol. To this was added one-half mole of the appropriate N-alkylthiourea and 68 g. (0.5 mole) of 1-ethoxyethylidinemalononitrile. The reaction was complete after standing in a stoppered flask for three days. The solution was concentrated and diluted with water as in the above experiments. When acidified with acetic acid, the product crystallized. The resulting 5-cyano-3,6-dialkyl-2-thiocytosine was collected, dried in air, and recrystallized from a mixture of ethyl alcohol and N,N-dimethylformamide.

(12) J. P. Vila and R. G. Jarque, *Anales fis. y quim.* (*Spain*), **40**, 402 (1944); *C. A.*, **39**, 4329 (1945)].

5-Benzoyl-2-thiouracils (Table I).—One-tenth mole of the appropriate thiourea was added to 250 ml. of absolute ethanol containing 0.1 mole of sodium ethylate. To this was added 24.8 g. (0.1 mole) of ethyl ethoxymethylenebenzoylacetate.[13] This was set aside for 3 days. The alcohol was partially evaporated, cold water was added and the product precipitated by addition of acetic acid. The 5-benzoyl-2-thiouracils were recrystallized from ethanol.

5-Acetyl-2-thiouracils (Table I).—Two-tenths mole of the thiourea was treated with 30.4 g. (0.2 mole) of ethyl ethoxymethyleneacetoactate[14] and 0.2 mole of sodium ethylate in the manner described in the above paragraph. The resulting 5-acetyl-2-thiouracils were recrystallized from a mixture of ethanol and ethyl acetate.

5-Acetyl-3-β-methoxyethyl-2-methylthio-4(3H)-pyrimidinone.—A solution was made of 11.4 g. (0.05 mole) of 5-acetyl-3 β-methoxyethyl-2-thiouracil in 60 ml. of 2 *N* NaOH. This was stirred and 7.1 g. (0.05 mole) of methyl iodide was added dropwise. After standing for two hours at room temperature, the solid was collected and recrystallized from a mixture of ethyl acetate and light petroleum ether; yield 5 g. (41%), m.p. 94°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3S$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.91; H, 5.87; N, 11.70.

5-Acetyl-3-isopropyl-2-methylthio-4(3H)-pyrimidinone.—To 100 ml. of methanol was added 21 g. (0.1 mole) of 5-acetyl-3-isopropyl-2-thiouracil, 5.4 g. (0.1 mole) of sodium methylate and 14.1 g. (0.1 mole) of methyl iodide. The solution was allowed to stand for several hours and then evaporated to dryness on the steam-bath. The sodium iodide was separated by the addition of ether. The filtrate was evaporated to yield an oil which crystallized upon standing. This was recrystallized three times from light petroleum ether; yield 12 g. (53%).

(13) L. Panizzi, *Gazz. chim. ital.*, **73**, 13 (1943) [*C. A.*, **39**, 1871 (1945)].

(14) L. Claisen, *Ann.*, **297**, 16 (1897).

Anal. Calcd. for $C_{10}H_{14}N_2O_2S$: N, 13.33. Found: N, 13.57.

5-Carbethoxy-2-methylthio-3-phenyl-4(3H)-pyrimidinone.—To 200 ml. of 2% aqueous sodium hydroxide was added 27.6 g. (0.1 mole) of 5-carbethoxy-3-phenyl-2-thiouracil. The mixture was stirred mechanically and the solid dissolved. To this was added, dropwise, 12.6 g. (0.1 mole) of dimethyl sulfate. After 0.5 hour the product had separated. This solid was collected, dried and recrystallized from ethyl acetate; yield 28 g. (96%), m.p. 128°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.76; H, 4.94; N, 9.61.

5-Cyano-3-isopropyl-2-thiouracil.—Five grams of 5-cyano-3-isopropyl-2-thiocytosine was added to 35 ml. of 3 *N* HCl. The acid solution was refluxed for 3 hours. The mixture was cooled and the insoluble 5-cyano-3-isopropyl-2-thiouracil was collected and recrystallized from ethyl alcohol; yield 4 g. (80%), m.p. 84–85°.

Anal. Calcd. for $C_8H_9N_3OS$: C, 49.23; H, 4.65; S, 16.40. Found: C, 48.99; H, 5.14; S, 16.39.

Alkaline Hydrolysis of 5-Carbethoxy-2-thiouracils.—Ten grams of the 5-carbethoxy-2-thiouracil was boiled with 50 ml. of 3 *N* NaOH for 2–4 hours. The cooled solution was filtered and the filtrate acidified with dilute hydrochloric acid. The product was collected and recrystallized from ethanol. The following 5-carboxythiouracils were obtained in yields of 50–75%.

5-Carboxy-3-phenyl-2-thiouracil, m.p. 248° dec. *Anal.* Calcd. for $C_{11}H_8N_2O_3S$: C, 53.23; H, 3.25. Found: C, 53.31; H, 3.45.

5-Carboxy-3-*n*-hexyl-2-thiouracil, m.p. 154°. *Anal.* Calcd. for $C_{11}H_{16}N_2O_3S$: S, 12.52; N, 10.93. Found: S, 12.65; N, 10.72.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY AND SOCONY MOBIL OIL CO., INC., RESEARCH AND DEVELOPMENT LABORATORY]

Disubstituted Phosphine Oxides. III. Addition to α,β-Unsaturated Nitriles and Carbonyl Compounds[1]

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Two disubstituted phosphine oxides have been added to α,β-unsaturated nitriles, esters, ketones and amides in the presence of traces of sodium ethoxide. Hydrolysis of the nitrile, ester and amide adducts gave 3-disubstituted phosphinylpropionic acids (V). Similar additions to diethyl maleate and hydrolysis gave 1-disubstituted phosphinylsuccinic acids which can be decarboxylated to form V.

Unsymmetrical tertiary phosphine oxides have been prepared by the base-catalyzed addition of two disubstituted phosphine oxides (I) to α,β-unsaturated nitriles, esters, ketones and an amide. Analogous reactions of the structurally similar dialkyl phosphonates (II)[4] have been reported by Pudovik[5] and others.[6] II has been added to α,β-unsaturated nitriles[5a–c,6] esters[5a,b,d–f,6] amides[5e,g] and ketones.[5a,h,6]

While a few of the additions were carried out with di-*n*-octylphosphine oxide (Ia),[7,8] most of the reactions involved a previously unreported analog, dibenzylphosphine oxide (Ib). Because of the greater ease of removal of the less soluble higher melting dibenzylphosphine oxide adducts from the reaction mixture, the yields were higher than for similar di-*n*-octylphosphine oxide addition products. The dibenzylphosphine oxide was prepared

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(3) Taken from a thesis submitted by J. S. B. to the Department of Chemistry, Temple University, in partial fulfillment of the requirements for the degree of Master of Arts.

(4) The nomenclature of organophosphorus compounds used in this paper follows that outlined in *Chem. Eng. News*, **30**, 4515 (1952).

(5) A few of the many papers by Pudovik and co-workers are as follows: (a) A. N. Pudovik and B. A. Arbuzov, *Doklady Akad. Nauk S.S.S.R.*, **73**, 327 (1950); *C.A.*, **45**, 2853 (1951); (b) *J. Gen. Chem. U.S.S.R.*, **21**, 2035 (1951); (c) A. N. Pudovik and N. I. Plakatina, *Sbornik Statei Obshchei Khim.*, **2**, 831 (1953); *C. A.*, **49**, 6821 (1955); (d) A. N. Pudovik, *Zhur. Obshchei Khim.*, **22**, 1143 (1952); *C. A.*, **47**, 4836 (1953); (e) A. N. Pudovik and D. Kh. Yarmukhametova, *Izvest. Akad. Nauk, S.S.S.R., Otdel. Khim. Nauk*, 721 (1952); *C. A.*, **47**, 10467 (1953); (f) A. N. Pudovik, *ibid.*, 926 (1952); *C. A.*, **47**, 10467 (1953); (g) A. N. Pudovik, *Doklady Akad. Nauk S.S.S.R.*, **85**, 349 (1952); *C. A.*, **47**, 5351 (1953); (h) A. N. Pudovik, *Zhur. Obshchei Khim.*, **22**, 1371 (1952); *C. A.*, **47**, 4837 (1953).

(6) B. Bochwic and J. Michalski, *Nature*, **167**, 1035 (1951).

(7) R. H. Williams and L. A. Hamilton, THIS JOURNAL, **74**, 5418 (1952).

(8) R. H. Williams and L. A. Hamilton, *ibid.*, **77**, 3411 (1955).