[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

Carbamates and Ureas Derived from Amino- and Oxopyrimidines[1,2]

ELIZABETH DYER, MARTIN L. GLUNTZ, AND ELINOR J. TANCK

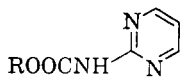
Received August 14, 1961

By reaction of aminopyrimidines with chloroformates, the methyl, ethyl, 1-pentyl, and phenyl esters of both 2- and 4-pyrimidinecarbamic acid have been prepared. Treatment of 5-aminouracil with chloroformates yielded the methyl, ethyl, and 1-pentyl esters of uracil-5-carbamic acid as well as, in the last case, an isomeric compound, presumably an *N*-1-carbopentoxy derivative of 5-aminouracil. Uracil itself reacted with chloroformates to give the methyl, ethyl, and 1-pentyl esters of uracil-1-carboxylic acid.

The action of phenyl isocyanate on cytosine gave 1-phenyl-3-[4-(2-hydroxypyrimidyl)]urea, not a urea-carbamate as recorded in the literature. Isocytosine, 2-aminopyrimidine, and 4-aminopyrimidine similarly yielded 1-phenyl-3-pyrimidylureas.

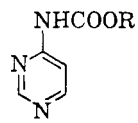
Since ethyl carbamate (urethan) is of benefit[3] in treating granulocytic leukemia, and combinations of urethan with certain pyrimidines have some inhibitory effect on tumors,[4] it seemed worthwhile to investigate pyrimidine carbamates. There are few known compounds in which the carbamate nitrogen is directly attached to the pyrimidine ring. A few examples in which the pyrimidine ring is unoxygenated are all derivatives of 5-pyrimidinecarbamates.[5-7] There are two monooxopyrimidine carbamates (4-oxo-5-pyrimidinecarbamates).[8,9] Biltz and co-workers[10] prepared several 2,4,6-trioxo- and 2,4-dioxopyrimidine carbamates from 5-aminobarbituric acid and 5,6-diaminouracil.

In the current work carbamates of unsubstituted pyrimidines were prepared by treating 2-aminopyrimidine and 4-aminopyrimidine with methyl, ethyl, 1-pentyl, and phenyl chloroformates, giving compounds I–VIII (Table I).



2-Pyrimidinecarbamates

I. R = CH_3
II. R = C_2H_5
III. R = $(CH_2)_4CH_3$
IV. R = C_6H_5



4-Pyrimidinecarbamates

V. R = CH_3
VI. R = C_2H_5
VII. R = $(CH_2)_4CH_3$
VIII. R = C_6H_5

The reaction of the 2-aminopyrimidine with the chloroformates could be accomplished either in aqueous medium with sodium hydroxide or in refluxing benzene solution with an excess of the pyrimidine as hydrogen chloride acceptor. The 4-aminopyrimidine reacted only under the latter conditions. 2,6-Dimethyl-4-aminopyrimidine did not react in either medium. This is surprising in view of the fact that von Meyer[5] obtained a carbamate by reaction of 2,6-diethyl-5-methyl-4-aminopyrimidine with ethyl chloroformate. Work is being continued on the reactivity of the substituted aminopyrimidines.

The structure of compounds V and VI was proved by an independent synthesis from the hydrazide[11] of 4-pyrimidinecarboxylic acid[12] by conversion to the azide followed by rearrangement in methanol and in ethanol.

Efforts to establish the structure of the carbamates derived from 2-aminopyrimidine by reduction with lithium aluminum hydride were unsuccessful. These carbamates are assumed to have the structures shown (I–IV), because they can be prepared under the same reaction conditions as the 4-pyrimidinecarbamates and because of similarities in infrared spectra. The spectra are distinguished by an intense band in the region of 1740 $cm.^{-1}$ and by the lack of N—H bands at 3400 and 1650 $cm.^{-1}$

5-Aminopyrimidine was unreactive to chloroformates, although it forms an acetyl derivative.[13] The very low basicity of this compound[13] (pK_a = 2.6) may be the cause. An unsuccessful attempt was made to secure a carbamate of 5-aminopryimidine through the rearrangement of pyrimidine-5-carboxamide[14] with sodium methoxide and bromine

(1) This investigation was supported by PHS Grant No. CY-3477 from the National Cancer Institute, Public Health Service.

(2) From the Ph.D. thesis of Martin L. Gluntz, 1960, and the M.S. thesis of Elinor J. Tanck, 1959.

(3) A. Haddow and W. A. Sexton, *Nature*, **157**, 500 (1946).

(4) G. B. Elion, S. Bieber, H. Nathan, and G. H. Hitchings, *Cancer Research*, **18**, 802 (1958).

(5) E. von Meyer, *J. prakt. Chem.*, [2], **30**, 116 (1884).

(6) (a) R. Urban and O. Schnider, *Helv. Chim. Acta*, **41**, 1806 (1958); (b) Hoffmann-La Roche and Co., British Patent **800,776** (1958).

(7) S. Sugasawa, S. Akahoshi, S. Toda, and H. Tomisawa, *J. Pharm. Soc. Japan*, **72**, 192 (1952); *Chem. Abstr.*, **47**, 6418 (1953).

(8) W. Huber and H. A. Holscher, *Ber.*, **71**, 87 (1938).

(9) T. B. Johnson, *Am. Chem. J.*, **34**, 941 (1905).

(10) H. Biltz *et al.*, *Ann.*, **426**, 237, 246, 269 (1922); *Ber.*, **58B**, 2193 (1925).

(11) H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry, and J. Bernstein, *J. Am. Chem. Soc.*, **75**, 1935 (1953).

(12) S. Gabriel and J. Colman, *Ber.*, **32**, 1536 (1899).

(13) N. W. Whittaker, *J. Chem. Soc.*, 1565 (1951).

(14) M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1218 (1951).

TABLE I

PYRIMIDINE CARBAMATES

No.	R[a]	M.P.[b]	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
				ESTERS OF 2-PYRIMIDINECARBAMIC ACID						
I	Methyl	134–136	45	$C_6H_7N_3O_2$	47.02	4.62	27.45	47.07	4.88	27.85
II	Ethyl	116–117	42	$C_7H_9N_3O_2$	50.28	5.44	25.14	50.39	5.41	25.32
III	1-Pentyl	111–112	27	$C_{10}H_{15}N_3O_2$	57.50	7.24	20.01	57.42	7.34	19.66
IV	Phenyl	154–155	11	$C_{11}H_9N_3O_2$	61.50	4.22	19.57	61.32	4.56	19.58
				ESTERS OF 4-PYRIMIDINECARBAMIC ACID						
V	Methyl	181–182	36	$C_6H_9N_3O_2$	47.02	4.62	27.45	47.02	4.47	26.97
VI	Ethyl	167–168	49	$C_7H_9N_3O_2$	50.28	5.44	25.14	50.45	5.85	24.87
VII	1-Pentyl	89–90	2	$C_{10}H_{15}N_3O_2$	57.50	7.24	20.01	57.35	7.16	19.96
VIII	Phenyl	203–204	20	$C_{11}H_9N_3O_2$	61.50	4.22	19.57	60.86	4.15	19.67
				ESTERS OF 2,4-DIOXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBAMIC ACID						
IX	Methyl	293–294 dec.	97	$C_6H_7N_3O_4$	38.91	3.84	22.69	39.04	3.59	22.35
X	Ethyl	223–224	70	$C_7H_9N_3O_4$	42.20	4.57	21.09	42.88	4.96	20.89
XI	1-Pentyl	212–213	45	$C_{10}H_{15}N_3O_4$	49.78	6.28	17.41	49.50	6.11	17.40
XII	Isomer[c]	99–100	15	$C_{10}H_{16}N_3O_4$	49.78	6.28	17.41	50.01	6.58	17.25
				ESTERS OF 2,4-DIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE-1-CARBOXYLIC ACID						
XIII	Methyl	192–195 dec.	65[d]	$C_6H_6N_2O_4$	42.36	3.56	16.47	42.24	3.62	16.50
XIV	Ethyl	130–132	35[d]	$C_7H_8N_2O_4$	45.64	4.39	15.21	45.57	4.55	15.28
XV	1-Pentyl	127–128	51[d]	$C_{10}H_{14}N_2O_4$	53.08	6.25	12.38	52.97	6.07	12.59

[a] Radical of —COOR. [b] Corrected. [c] Believed to be 2,4-dioxo-1,2,3,4-tetrahydro-1-(carbo-1-pentoxy)-5-aminopyrimidine. [d] Based on recovered starting material.

TABLE II

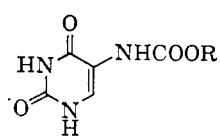
1-PHENYL-3-PYRIMIDYLUREAS OBTAINED FROM THE REACTION OF PHENYL ISOCYANATE WITH AMINO AND AMINOOXOPYRIMIDINES

Cpd. No.	Name	Yield, %	Dec. Temp.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
XVI	1-Phenyl-3-(4-pyrimidyl)-urea	42	234–236	$C_{11}H_{10}N_4O$	61.67	4.71	26.16	61.36	4.63	25.97
XVII	1-Phenyl-3-(2-pyrimidyl)-urea	48	225–227	$C_{11}H_{10}N_4O$	61.67	4.71	26.16	61.21	4.64	25.97
XVIII	1-Phenyl-3-[2-(4-hydroxypyrimidyl)]urea	34	260.5–262.5	$C_{11}H_{10}N_4O_2$	57.38	4.38	24.34	57.39	4.33	24.24
XIX	1-Phenyl-3-[4-(2-hydroxypyrimidyl)]urea	30	266–267	$C_{11}H_{10}N_4O_2$	57.38	4.38	24.34	56.78	4.72	24.58
	2:1 Adduct of C_6H_5NCO and cytosine, Wheeler and Johnson[a]		260, sintered 250	$C_{18}H_{10}N_5O_3$			20.05			20.4

[a] See ref. 21.

in methanol as described for 2,4-dimethyl-5-carboxamide.[6b] An attempt to use the Curtius rearrangement failed at the point of converting methyl pyrimidine-5-carboxylate to the hydrazide.

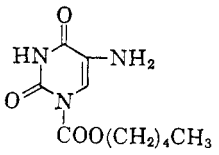
Treatment of 5-aminouracil with methyl, ethyl, and 1-pentyl chloroformates in the presence of aqueous base gave good yields of the methyl, ethyl, and 1-pentyl esters of 1,2,3,4-tetrahydro-2,4-dioxo-5-pyrimidinecarbamic acid, IX, X, and XI.



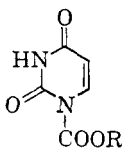
IX. R = CH_3
X. R = C_2H_5
XI. R = $(CH_2)_4CH_3$

In addition to the normal product XI (in 45% yield), an isomeric substance, XII was obtained in 15% yield from the reaction of 5-aminouracil with 1-pentyl chloroformate. Compound XII, unlike XI, was soluble in ligroin and only sparingly soluble in water. The infrared spectrum of XII showed two distinct bands at 1760 cm.$^{-1}$ and at 1670 cm.$^{-1}$, while the normal product had one broad band between 1740 and 1640 cm.$^{-1}$. A tentative assignment of structure to XII is that of an *N*-1-carbopentoxy derivative of 5-aminouracil.

Support for structure XII comes from the finding that uracil reacts with methyl, ethyl, and 1-pentyl chloroformates to give compounds XIII, XIV, and XV, respectively. The medium for the



XII



XIII. R = CH_3
XIV. R = C_2H_5
XV. R = $(CH_2)_4CH_3$

reaction, aqueous sodium hydroxide, was the same as for preparing compound XII. Compounds XIII, XIV, and XV were also obtained by treating the anhydrous sodium salt of uracil with each of the three chloroformates in refluxing benzene. Infrared absorption of these compounds was at 1775–1795 and at 1710–1720 cm.$^{-1}$ Since the product of treating uracil with acetic anhydride was proved to be the *N*-1-derivative,[15] it is reasonable to suggest that compounds XII–XV probably have the carboalkoxy group in the *N*-1-position. Like *N*-1-acetyluracil,[15] these carboalkoxyuracils are hydrolyzed by water, giving uracil.

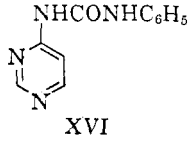
An unsuccessful attempt was made to prepare a carbamate from 6-aminouracil. This result is in accord with the findings of Biltz and co-workers,[10] who observed that, in 5,6-diaminouracil, the 5-amino, but not the 6-amino group reacted with methyl or ethyl chloroformate. In the current work the aminooxopyrimidines cytosine and isocytosine also failed to yield carbamates with ethyl chloroformate. (Cytosine did not react and isocytosine gave an intractable mixture.) The inactivity of isocytosine toward acylation was observed previously,[16] and the decrease in basicity of 4-aminopyrimidine by introducing an oxygen at the 2-position (giving cytosine) has been explained by Brown and Harper.[17]

Compound I–IV and IX–XI were tested by the Cancer Chemotherapy National Service Center (their numbers 30087–30090 and 36429–36431) and were found to be nontoxic and inactive toward various mouse tumors. The first four compounds were tested against Sarcoma 180, Leukemia 1210, and Ehrlich Ascites; the others against Sarcoma 180, Carcinoma 755, and Leukemia 1210. Compound XI also showed no cytotoxicity toward the KB tissue culture cell line.

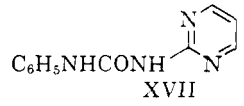
The possibility of preparing carbamates of the structure $C_6H_5NHCOOR$, where OR is a hydroxypyrimidine radical, was also investigated. The reaction of phenyl isocyanate with oxopyrimidines was tried in the presence of basic catalysts, in the hopes of promoting enolization and rapid reaction with the resulting hydroxyl groups. It was found, however, that 4-methyl-6-hydroxypyrimidine[18] did not react with phenyl isocyanate in benzene solution at reflux in the presence of pyridine, triethylamine, or copper naphthenate as catalyst, nor with excess isocyanate as solvent at 100°. Similarly 2-hydroxypyrimidine[19] and uracil were unreactive. (Basic catalysts could not be used at the higher temperatures because the predominant reaction was then polymerization of the isocyanate.) It is apparent that the preference[20] of these pyrimidines for the keto form cannot be overcome by the conditions used.

For comparison with the oxopyrimidines, the behavior of the oxoaminopyrimidines cytosine and isocytosine toward phenyl isocyanate was investigated. Wheeler and Johnson described[21] a reaction product from cytosine which contained two equivalents of phenyl isocyanate. Since a diadduct might have one carbamate and one urea group, the Wheeler and Johnson procedure was repeated. The product obtained, although similar in properties to the reported diadduct, was a monoadduct (compound XIX in Table II). Similarly, a monoadduct XVIII was obtained from isocytosine and phenyl isocyanate. Johnson, Johns, and Heyl[22] obtained a monoadduct from phenyl isocyanate and 5-nitrocytosine.

In view of the greater reactivity of amino than hydroxyl groups toward isocyanates, these monoadducts XVIII and XIX were expected to be ureas rather than carbamates. This was confirmed by spectral evidence. For comparison, the new[23] phenylurea derivatives XVI and XVII were synthesized by reaction of 4-aminopyrimidine and 2-aminopyrimidine respectively, with phenyl isocyanate.



XVI



XVII

The urea derivatives XVI and XVII showed carbonyl absorption at 1690 cm.$^{-1}$, while the phenyl ester of 2-pyrimidinecarbamic acid (IV) showed a strong band at 1750 cm.$^{-1}$ The phenyl isocyanate adducts from cytosine and isocytosine

(15) L. B. Spector and E. B. Keller, *J. Biol. Chem.*, **232**, 185 (1958).

(16) G. W. Raiziss and M. Freifelder, *J. Am. Chem. Soc.*, **64**, 2340 (1942).

(17) D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1298 (1961).

(18) Prepared by the method of R. R. Williams, A. E. Ruehle, and J. Finkelstein, *J. Am. Chem. Soc.*, **59**, 528 (1937).

(19) Prepared by the method of D. J. Brown, *Nature*, **165**, 1010 (1950).

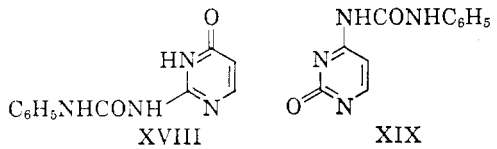
(20) M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 3716 (1952); A. Albert and E. Spinner, *J. Chem. Soc.*, 1221 (1960).

(21) H. L. Wheeler and T. B. Johnson, *Am. Chem. J.*, **29**, 501 (1903).

(22) T. B. Johnson, C. O. Johns, and F. W. Heyl, *Am. Chem. J.*, **36**, 168 (1906).

(23) Compound XVII was mentioned as tested by R. E. Thompson, D. F. Walker, and M. C. Dunn in *J. Am. Pharm. Assoc.*, **42**, 647 (1953), but no report of its preparation or properties has been found.

both had strong bands at 1690 and 1650 cm.$^{-1}$ Since unsubstituted cytosine and isocytosine have carbonyl absorption at 1650 cm.$^{-1}$, it is reasonable to assume that the band at 1690 cm.$^{-1}$ in the isocyanate adducts is due to urea carbonyl. Hence these adducts, which are new compounds, have the following structures:



XVIII XIX

EXPERIMENTAL

Pyrimidinecarbamates. The carbamates were prepared either by (A) the dropwise addition of an aqueous solution containing 1.0 equivalent of the aminopyrimidine and 1.2 equivalents of sodium hydroxide to 1.0 equivalent of the stirred chloroformate ester[24] at 40° or by (B) adding 0.5 equivalent of the chloroformate slowly to a refluxing benzene solution of 1.0 equivalent of the aminopyrimidine. Compounds I–IV could be obtained by either method, compounds V–VIII by method B only, and compounds IX–XIV by method A.

In method A the carbamate was separated by extraction (often continuous) with ether or chloroform. The extracts were dried and evaporated and the residues recrystallized several times from benzene, ethyl acetate, or mixtures of benzene–ligroin or ethyl acetate–ligroin. Sometimes purification could be best effected by column chromatography on alumina with benzene or a 1:1 benzene–ethyl acetate mixture. Compounds IX–XI were recrystallized from water. The carbamates XIII–XV were separated from unchanged uracil by extraction with cold acetone.

In method B the hydrochloride of the aminopyrimidine precipitated first and the product was obtained by evaporation of the benzene filtrate.

Pyrimidine-4-carboxamide. A solution of 0.20 g. of ethyl pyrimidine-4-carboxylate[25] in 5 ml. of absolute ethanol saturated with ammonia yielded, after 24 hr., 0.11 g. of needles, m.p. 191–192°. An additional 0.04 g. was obtained from the filtrate, giving a total yield of 94%. The melting point was unchanged after sublimation.

Anal. Calcd. for $C_5H_5N_3O$: C, 48.78; H, 4.11; N, 34.14. Found: C, 48.69; H, 4.30; N, 33.87.

Attempts to convert this amide to a carbamate by use of bromine and sodium methoxide in methanol were unsuccessful.

Pyrimidine-4-carboazide. By use of Sah and Woo's procedure,[26] 0.50 g. of pyrimidine-4-carbohydrazide[11] was converted to the new carboazide in 67% yield. The azide melted at 50–51°, with decomposition at 80–90°.

Anal. Calcd. for $C_5H_3N_5O$: C, 40.27; H, 2.03; N, 46.98. Found: C, 40.18; H, 1.99; N, 46.57.

Treatment of this azide with methanol and ethanol in the cold followed by refluxing gave products identical with V and VI, as shown by mixed melting points and spectra.

Picrates. The carbamates derived from 2-aminopyrimidine, with the exception of compound II gave only the picrate of 2-aminopyrimidine,[27] when treated with aqueous picric acid. In contrast, the carbamates derived from 4-aminopyrimidine (whose picrate is known)[28] gave new picrates when treated, in aqueous acid solution, with picric acid. None of the carbamates derived from uracil gave a picrate. The picrates were recrystallized from water; satisfactory analyses were obtained. The melting points were as follows: picrate of compound II, 157–159°; V, 195–197°; VI, 196–200°; VII, 135–137°; VIII, 172–174° dec.

1-Phenyl-3-pyrimidylureas. Compound XIX was prepared by heating 0.5 g. (0.0043 mole) of anhydrous cytosine with 0.5 ml. (0.0046 mole) of phenyl isocyanate at 100° for 6 hr. in a flask protected from moisture. Ethanol (20 ml.) was then added to combine with unchanged isocyanate, and the mixture refluxed 1 hr. After removal of the alcohol, the hot alcohol extraction was repeated. The residue was twice extracted with boiling water. The residue, after recrystallization from *N,N*-dimethylformamide, consisted of 0.3 g. (30%) of a crystalline product which decomposed at 266–267° and was insoluble in water, alcohol, acetone, benzene, chloroform, and dioxane. (The extracts yielded only ethyl *N*-phenylcarbamate.)

When the reaction with cytosine was carried out with 2 equivalents of phenyl isocyanate in dimethylformamide solution at 50°, 74% of the cytosine was recovered unchanged.

Compounds XVI, XVII, and XVIII were prepared by similar procedures from 4-aminopyrimidine,[29] 2-aminopyrimidine, and isocytosine and phenyl isocyanate with no solvent. In the case of XVII, room temperature for 45 hr. rather than 100° for 6 hr. gave better results because of decomposition of the 2-aminopyrimidine at the higher temperature.

NEWARK, DEL.

(24) Kindly supplied by Food Machinery and Chemical Corp.; redistilled before use.

(25) G. Carrara, F. M. Chiancone, F. D'Amato, E. Ginoulhiac, C. Martinuzzi, U. M. Teotino, and N. Visconti, *Gazz. chim. ital.*, **82**, 652 (1952); *Chem. Abstr.*, **48**, 6424 (1954).

(26) P. P. T. Sah and T. F. Woo, *Rec. trav. chim.*, **58**, 1013 (1939).

(27) H. L. Wheeler, *J. Biol. Chem.*, **3**, 290 (1907).

(28) E. Buttner, *Ber.*, **36**, 2229 (1903).

(29) D J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950).