By refluxing IIa′ with phenyl isocyanate in benzene for 2 hr. the adduct was obtained.

(b) *Reaction of O-p-tolyl-N,N-ethyleneurethane* (Ie) *with p-phenetidine at 0°.* A 1.77-g. sample (0.010 mole) of Ie and 1.37 g. (0.010 mole) of *p*-phenetidine were mixed together at 0°, and stored in a refrigerator for a week. By recrystallization of the product from ether and alcohol, 2.5 g. (80%) of IIe′, melting at 120–122°, was obtained. Infrared absorption spectra of IIe′ showed a strong carbonyl absorption band at 1701 cm.$^{-1}$, and NH band at 3349 cm.$^{-1}$.

At 35°. A 1.77-g. sample of Ie and 1.37 g. of *p*-phenetidine were mixed at 35° and stored in a thermostat kept at 35°. After 4 days, the crude product was recrystallized from alcohol. Fine needles, melting at about 140° (IVe′), were obtained, weighing 0.8 g. From the alcoholic filtrate, 1.8 g. (56%) of IIe′, melting at about 120°, was obtained.

IVe′ was recrystallized from alcohol and melted at 141–142°. Infrared absorption spectra of IVe′ showed a strong absorption band at 1695 cm.$^{-1}$, (C=O), and of NH at 3311 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{33}N_3O_5$: C, 68.41; H, 6.79. Found: C, 67.71; H, 6.70. Molecular weight determined by Akiya's method[19] was nearly 490. (Calcd.: 491.)

By the reaction of 220 mg. of Ie and 400 mg. of IIe′ in toluene at 35°, 450 mg. of IVe′ was obtained. IVe′ reacted with diethylamine to give presumably *N,N*-bis(β-diethylureido)ethyl-*p*-phenetidine, m.p. 124–125°.

Anal. Calcd. for $C_{22}H_{39}N_5O_3$: C, 62.68; H, 9.33; N, 16.61. Found: C, 62.50; H, 9.39; N, 17.06.

At 75°. A 1.77-g. sample of Ie and 1.37 g. of *p*-phenetidine were mixed at 75°, and stored in a thermostat kept at 75°. After an hour, crystals began separating. After 24 hr., the sticky crude product (presumably polymerization of Ie took place in part) was recrystallized from alcohol. Glittering flakes, melting at 210° (III′), were obtained first. After filtration of III′, the alcoholic solution was concentrated gradually, and an additional crop of III′ was filtered, and the filtrate was again concentrated. As soon as fine needle crystals began separating, the solution was cooled gradually. IVe′ was thus obtained. After removing IVe′ and evaporating the alcohol, the residue was recrystallized from ether. Thus IIe′ was obtained.

III′ weighed 0.4 g. (19%) and melted at 210°. IVe′ weighed 0.3 g. (6%) and melted at 140°. IIe′ weighed 0.3 g. (10%) and melted at 120°.

(c) *Reaction of O-p-nitrophenyl-N,N-ethyleneurethane* (Ig) *with p-toluidine, at 0°.* To a solution of 0.54 g. (0.005 mole) of *p*-toluidine in 2 ml. of toluene, 1.04 g. (0.005 mole) of finely powdered Ig was added at 0°. Ig remained undissolved in part. The mixture was then stored in a refrigerator. After a month, ether was added to the sticky contents, when 0.2 g. of Ig was recovered unchanged. Evaporation of the solvent gave a yellow polymer-like residue from which 0.3 g. (20%) of IIg″, melting at 108–109° with brown coloration, was extracted with ether.

At 35°. To a solution of 1.07 g. (0.010 mole) of *p*-toluidine in 1 ml. of toluene, 2.08 g. (0.010 mole) of Ig was added at 35°. Ig gradually dissolved. After the mixture had stood at 35° for 4 days, the contents were recrystallized from alcohol. III″, 0.3 g. (17%) melting at 193° was obtained as flakes, and then from the filtrate, about 0.2 g. (6%) of IIg″, melting at 108° with brown coloration, was obtained.

An example of the reaction of ethyleneurethane with amine in dioxane at 55°. Reaction of O-p-nitrophenyl-N,N-ethyleneurethane (Ig) *with p-phenetidine.* A 1.04-g. sample (0.005 mole) of Ig and 0.69 g. (0.005 mole) of *p*-phenetidine in 10 ml. of dioxane were allowed to stand at 55° for 48 hr. Fine flakes, melting at 210° (III′), were filtered, and the filtrate was concentrated under reduced pressure. An additional crop of III′ was filtered and the filtrate was again concentrated to dryness. The residue was a polymer-like substance from which pure compound was not obtained by extraction with ether. The yield of III′ was 440 mg. (43%).

An example of conversion of a type II *compound to a type* III *in refluxing pyridine. O-p-Chlorophenyl-N-(β-p-phenetidinoethyl)-urethane* (IIh′). A 100-mg. sample of IIh′ was refluxed in 1 ml. of pyridine for 1 hr. After the pyridine was removed by distillation under reduced pressure, the residue was recrystallized from alcohol. A 20-mg. sample (32%) of III′, melting at 210°, was obtained first. From the filtrate, 50 mg. (50%) of IIh′ was recovered.

Conversion of IIh′ *in p-phenetidine.* A 100-mg. sample of IIh′ was allowed to stand in *p*-phenetidine, at 35° for 3 days, at 55° for 2 days, and at 65° for a day. In all cases, IIh′ was recovered unchanged. But at 70°, after a day, a small quantity of III′ was obtained with 70 mg. of IIh′.

A 340-mg. sample of IIh′ was allowed to stand in *p*-phenetidine at 75° for 24 hr. By addition of ether and alcohol, 160 mg. (76%) of III′, melting at 210°, was obtained. Attempts to recover IIh′ were unsuccessful.

Acknowledgment. The authors wish to express their thanks to Prof. Kunio Kozima for his advice in interpreting the results of infrared absorption spectra.

(19) S. Akiya, *J. Pharm. Soc. Japan*, **57**, 967 (1937).

TOKYO, JAPAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE PAINT DIVISION, PITTSBURGH PLATE GLASS COMPANY]

Reaction of Acrylamide and Pyridinium Chloride

ROSTYSLAW DOWBENKO

Received January 5, 1960

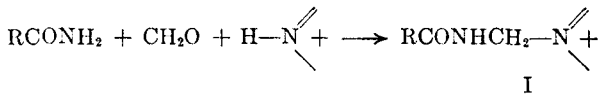
Acrylamide and pyridinium chloride react to give *N*-(2-carbamylethyl)pyridinium chloride, II, whose structure was proved by hydrogenation of it to the piperidinium analog which was synthesized independently. The reaction was extended to several other heterocyclic base salts and α,β-unsaturated amides.

Some time ago it was disclosed in a patent[1] that aliphatic amides, formaldehyde (or *N*-hydroxymethylamides) and salts of the tertiary heterocyclic bases react to form *N*-amidomethyl inium salts (I). More recently, Weaver and coworkers[2] investigated this reaction in more detail

(1) A. W. Baldwin and E. E. Walker, U. S. Patent 2,146,392 (February 7, 1939).

(2) J. W. Weaver, H. A. Schuyten, J. G. Frick, Jr., and J. D. Reid, *J. Org. Chem.*, **16**, 1111 (1951).

and, for stearamidomethylpyridinium chloride, demonstrated several of its transformations. In

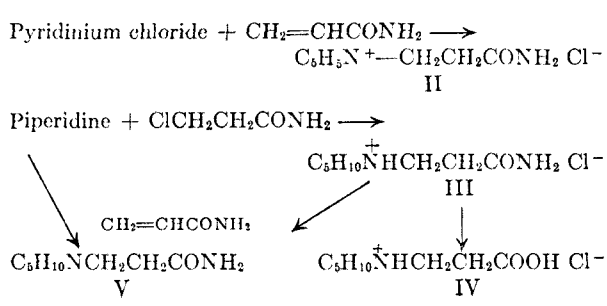


I

particular they studied reactions leading to *N*-alkoxymethylstearamides. In connection with other work done in these laboratories it was of interest to extend this reaction to acrylamide and other unsaturated amides in order to obtain compounds analogous to I. The reaction with acrylamide, however, took a different course and its examination forms the subject of this report.

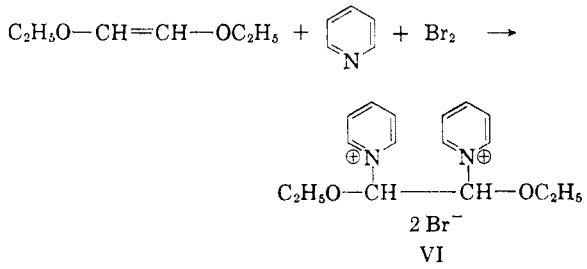
When an equimolar mixture of acrylamide, trioxane, and pyridinium chloride was heated at 65° in pyridine solution, there was obtained a solid, m.p. 197°, which was unreactive toward methanol under Weaver's conditions[2] and could be recovered from the reaction mixture. Similarly, when alcohols were substituted for pyridine as solvent, or when formaldehyde was replaced by acetaldehyde, butyraldehyde, or benzaldehyde, still the same compound was obtained. In contrast, from the reaction of *N*-(hydroxymethyl)acrylamide and pyridinium chloride under conditions[2] known to give compound I, only the starting materials were recovered. Finally, omission of the aldehyde from the reaction still gave the same compound above. These results clearly indicated that aldehydes did not participate in the reaction of acrylamide and that, therefore, *N*-acrylamidomethylpyridinium chloride was not formed, but instead an adduct of acrylamide and pyridinium chloride was obtained. This was confirmed by analysis which revealed an empirical formula $C_8H_{11}ClN_2O$ and showed no unsaturation. The latter finding was supported also by the fact that the compound was unreactive toward cyclopentadiene and did not polymerize on heating in the presence of ammonium persulfate in aqueous or methanolic solution. This information, along with the fact that the compound was salt-like (soluble in water and methanol, insoluble in ether, acetone, and hydrocarbons), led to assignment of the structure *N*-(2-carbamylethyl)pyridinium chloride (II).

Structure II was proved unequivocally by catalytic hydrogenation to a crystalline piperidinium compound (III), identical with that obtained directly from 3-chloropropionamide and piperidine.



Moreover, III could be transformed into the same free base (V) that was obtained by the addition of piperidine to acrylamide. Hydrolysis of III with hydrochloric acid yielded IV.

Addition of salts of heterocyclic bases to α,β-unsaturated carbonyl compounds has been reported on several occasions. Thus Barnett *et al.*[3] described addition of pyridine salts to benzoquinone, and Goerdeler[4] described addition of pyridine to maleic and acrylic acids from which the pyridinium betaines were obtained. The reaction of β-benzoylacrylic acid with pyridine[5] apparently is also of the same type and may be considered in effect a reaction of a pyridine salt.[6] Similarly, addition of pyridine to unsaturated compounds in the presence of halogens is also known and may be exemplified by the reaction of pyridine and 1,2-diethoxyethylene in the presence of bromine[7] in which compound VI is



VI

obtained. A recent example of interest is that reported by Heininger,[8] who found that cyanoethylation of pyrrolidinium chloride with acrylonitrile gives *N*-(2-cyanoethyl)pyrrolidinium chloride. The present case, however, apparently constitutes the first example of addition of pyridinium chloride to α,β-unsaturated amides.

In order to test the generality of this unusually facile addition of pyridinium chloride to acrylamide, several other compounds were used in the conditions under which the former gave the adduct II. The results are summarized in Table I and are

(3) E. de B. Barnett, J. W. Cook, and W. C. Peck, *J. Chem. Soc.*, **125**, 1035 (1924).

(4) J. Goerdeler, *Methoden d. org. Chemie* (*Houben-Weyl*), E. Müller, ed., Georg Thieme Verlag, Stuttgart, 1958, Vol. XI/2, p. 612. For similar reactions *cf.* also O. Lutz, *Ber.*, **43**, 2636 (1910); O. Lutz, *J. Russ. Phys. Chem. Soc.*, **47**, 1549 (1915); P. Pfeiffer and A. Langenberg, *Ber.*, **43**, 2926 (1910); P. Pfeiffer, *Ber.*, **47**, 1580 (1914); O. Lutz, R. Klein, and A. Jirgenson, *Ann.*, **505**, 307 (1933); O. Lutz and A. Krauklis, *Ber.*, **69**, 419 (1936); G. LaParola, *Gazz. Chim. Ital.*, **67**, 645 (1937); F. Bergmann, *J. Am. Chem. Soc.*, **60**, 2811 (1938); Y. Ogata, K. Tsunemitsu, and R. Oda, *Bull. Inst. Phys. Chem. Research* (Tokyo) Chem. Ed., **23**, 281 (1944); R. Adams and I. J. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952); C. D. Hurd and S. Hayao, *J. Am. Chem. Soc.*, **77**, 117 (1955).

(5) J. Bougault and P. Chabrier, *Compt. rend.*, **237**, 1420 (1953).

(6) *Cf.* also N. H. Cromwell, P. L. Creger, and K. E. Cook, *J. Am. Chem. Soc.*, **78**, 4412 (1956) for a more recent discussion of this work.

(7) H. Baganz, *Chem. Ber.*, **87**, 1373 (1954); *cf.* also ref. 3.

(8) S. A. Heininger, *J. Org. Chem.*, **22**, 704 (1957).

TABLE I

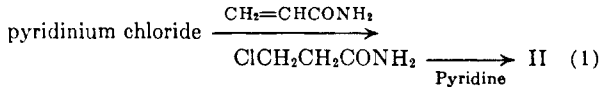
REACTION OF α,β-UNSATURATED AMIDES WITH HETEROCYCLIC SALTS[a]

Base	Amide	% Yield of Product[b]	M.P., °	Formula	Calcd. C	Calcd. H	Calcd. Cl	Calcd. N	Found C	Found H	Found Cl	Found N
Pyridine	Acrylamide	93	195–197	$C_8H_{11}ClN_2O$	51.48	5.94	19.00	15.01	51.69	5.77	18.81	14.78
									51.73	5.90	18.86	14.88
2-Methylpyridine	Acrylamide	93	171.5–172.5	$C_9H_{13}ClN_2O$	53.86	6.53	17.67	13.96	53.68	6.45	17.59	14.16
									53.77	6.69	17.61	14.12
2,6-Dimethylpyridine[c]	Acrylamide	—										
Quinoline	Acrylamide	82	199–200	$C_{12}H_{13}ClN_2O$	60.80	5.54	14.98	11.84	60.24	5.62	14.92	11.59
									60.04	5.83	14.61	11.70
Isoquinoline	Acrylamide	85	210.5–212	$C_{12}H_{13}ClN_2O$	60.80	5.54	14.98	11.84	61.17	5.47	15.07	11.59
									61.06	5.54	15.19	11.73
Phenanthridine	Acrylamide	84	234	$C_{16}H_{15}ClN_2O$	67.01	5.27	12.37	9.77	67.20	5.45	12.41	9.60
									67.09	5.36	12.38	9.58
Pyridine	Methacrylamide	38	205	$C_9H_{13}ClN_2O$	53.86	6.53	17.67	13.96	53.21	6.59	17.49	13.77
									53.33	6.57	17.46	13.91
Pyridine	Crotonamide	51	183–184	$C_9H_{13}ClN_2O$	53.86	6.53	17.67	13.96	53.03	6.57	17.46	13.91
									53.08	6.63	17.58	14.13

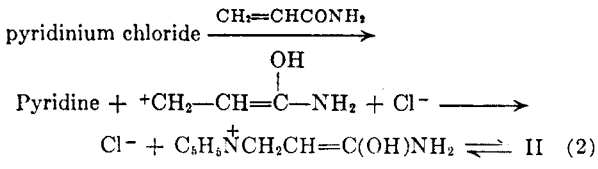
[a] According to the general procedure (Experimental). [b] Before recrystallization from a mixture of methanol and acetone. [c] 2,6-Dimethylpyridinium chloride was recovered unchanged.

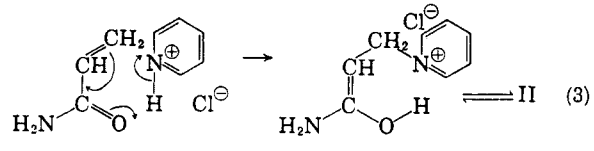
for the most part self-explanatory. It should be noted, however, that 2,6-dimethylpyridinium chloride was unreactive, and methacrylamide and crotonamide gave lower yields of the products. Although nonreaction of the former compound is probably due to steric hindrance in the 2,6-dimethylpyridinium ion, the lower yields from the latter are probably a real reflection of decreased reactivity of these compounds, although no attempts to obtain the best yields were made. Therefore, the facile addition of salts of heteroaromatic amines to α,β-unsaturated amides is quite general.

Several things may be said relating to the mechanism of this reaction, although no efforts were made to examine it in great detail. Two main paths appear to exist by which the reaction may proceed. The first (1) requires addition of hydrogen



chloride to acrylamide and subsequent alkylation of pyridine with the resulting 3-chloropropionamide. That the chloroamide is not an intermediate in the reaction, however, was demonstrated when 3-chloropropionamide and pyridine under the conditions of acrylamide reaction gave a very low yield of II.[9] An alternative mode of reaction is that represented by (2).[10] As required by this scheme, the reaction appears to be acid-catalyzed, and if this were valid the mechanism (2) is to be preferred. A still more attractive mechanism is the concerted one (3) involving the formation of a quasi six-membered ring.





EXPERIMENTAL[11]

Reaction of acrylamide and pyridinium chloride in the presence of trioxane. A solution of 71 g. (1.0 mole) of acrylamide, 116 g. (1.0 mole) of pyridinium chloride, 30 g. (1.0

(9) *Cf.* F. N. Hayes, H. K. Suzuki, and D. E. Peterson, *J. Am. Chem. Soc.*, **72**, 4524 (1950), for the failure to obtain *N*-(2-bromocyclohexyl)pyridinium bromide from 1,2-dibromocyclohexane on one hand, and its facile formation from cyclohexene, bromine, and pyridine on the other.

(10) For a similar formulation of the *cis-trans* interconversion of α, β-unsaturated ketones, *cf.* P. L. Southwick and R. J. Shozda, *J. Am. Chem. Soc.*, **81**, 8298 (1959).

(11) All melting points are uncorrected. Analyses by Dr. H. W. Galbraith, Knoxville, Tennessee.

mole) of trioxane, and 1 g. of hydroquinone in 500 ml. of methanol was refluxed for 3 hr. and then was allowed to stand at room temperature overnight. On concentration of the reaction mixture, dilution with acetone, and filtration there was obtained 175 g. (93%) of a hygroscopic white powder, m.p. 181–186°. Several recrystallizations from a mixture of methanol and acetone gave an analytical sample of II, m.p. 195–197°, as large needles grown in spheres.

Anal. Calcd. for $C_8H_{11}ClN_2O$: C, 51.48; H, 5.94; Cl, 19.00; N, 15.01. Found: C, 51.69, 51.73; H, 5.77, 5.90; Cl, 18.81, 18.86; N, 14.78, 14.88.

The compound was soluble in water and methanol, but insoluble in acetone, ether, ethyl acetate, and hydrocarbon solvents. It showed no unsaturation.

Substituting pyridine or butanol for methanol as solvent, or changing the aldehyde component to acetaldehyde, butyraldehyde, or benzaldehyde gave comparable yields of compound II. Omission of trioxane from the reaction mixture still gave compound II. None of II could be obtained from *N*-(hydroxymethyl)acrylamide and pyridinium chloride.

Compound II was recovered unchanged on heating with cyclopentadiene in methanol solution at 110° for 10 hr. Similarly, it was unchanged on refluxing its methanolic or aqueous solution 8 hr. in the presence of potassium persulfate.

A general procedure of reaction of heterocyclic amine hydrochlorides with α,β-unsaturated amides. To a solution of 0.20 mole of unsaturated amide and 0.20 mole of heterocyclic amine in 50 ml. of methanol is added with cooling a solution of 0.20 mole of dry hydrogen chloride in 50 ml. of methanol. The resulting solution is refluxed for 4 hr., filtered if necessary, and evaporated to about half of its original volume. It is then diluted with acetone and cooled. The product is isolated by filtration and purified by recrystallization from a mixture of methanol and acetone. Alternatively, the amine hydrochloride may be used instead of the free base and hydrochloric acid solution where more convenient.

Acrylamide and pyridinium chloride refluxing for 2 hr. gave about 85% of compound II. The yield was comparable when the reaction was run at room temperature for 1.5 hr.

Reaction of 3-chloropropionamide with pyridine. A solution of 15.8 g. (0.20 mole) of pyridine and 21.6 g. (0.20 mole) of 3-chloropropionamide[12] in 100 ml. of methanol was refluxed for 4 hr. and filtered. The filtrate was reduced in volume to 50 ml. and diluted with acetone. No crystallization occurred, but on standing at room temperature for over a week and further dilution with acetone the solution deposited 4.5 g. of a white solid, m.p. 185–188°, apparently compound II.

Reaction of acrylamide with pyridinium chloride with added acid and base. Three experiments were carried out using 0.20 mole of the two reactants in 50 ml. of methanol. The first was the control experiment. The second contained an additional 1 g. of pyridine and the third 5 ml. of concd. methanolic hydrogen chloride. All three runs were allowed to stand at room temperature for the same period of time; then they were diluted simultaneously with 20 ml. of acetone and allowed to stand in the cold for 1 hr. The quantities of the pyridinium compound II obtained were as follows (theoretical yield 37.4 g.): control, 6.2 g., m.p. 168–170°; pyridine added, 5.2 g., m.p. 168–171°; hydrogen chloride added, 9.1 g., m.p. 164–168°.

Hydrogenation of N-(2-carbamylethyl)pyridinium chloride (II). A solution of 19.9 g. (0.107 mole) of II in 200 ml. of methanol and 1.0 g. of 5% palladium on charcoal was shaken with hydrogen at an initial pressure of about 50 p.s.i. until 0.11 mole was absorbed. The catalyst was filtered off and the solvent removed almost completely. Addition of acetone caused separation of 18.5 g. of a cream-colored solid, m.p. 155–165°. Recrystallization from a mixture of methanol and acetone raised the m.p. to 172–175°, but further purification through recrystallization caused yellowing and decomposition.

When a solution of 18.5 g. (0.10 mole) of II in 200 ml. of methanol was shaken with 0.5 g. of platinum oxide until the pressure was constant, it absorbed in 1 hr. 105% of the theoretical 0.30 mole of hydrogen to give 17.0 g. (88.5%) of the piperidinium compound III. Several recrystallizations from a mixture of methanol and acetone gave the analytical sample, m.p. 196–197°.

Anal. Calcd. for $C_8H_{17}ClN_2O$: C, 49.86; H, 8.89; Cl, 18.40; N, 14.54. Found: C, 49.75; H, 9.14; Cl, 18.42; N, 14.60.

Hydrolysis of N-(2-carbamylethyl)piperidinium chloride (III). A mixture of 10.0 g. (0.052 mole) of III and 50 ml. of concd. hydrochloric acid was refluxed for 6 hr. Hydrochloric acid was removed by evaporating *in vacuo*, adding water and repeating the process several times. The residue was dissolved in a minimum amount of hot water, filtered, and allowed to crystallize. Filtration and recrystallization of the solid from aqueous acetone gave 7.0 g. (70%) of white shiny platelets of the acid IV, m.p. 210–212°. The analytical sample, prepared by several recrystallizations from the same solvent melted at 212–213°.

Anal. Calcd. for $C_8H_{16}ClNO_2$: C, 49.61; H, 8.33; Cl, 18.31; N, 7.23. Found: C, 50.03, 49.84; H, 8.40, 8.36; Cl, 17.05, 17.26; N, 7.04, 6.88.

Preparation of N-(2-carbamylethyl)piperidinium chloride (III). A solution of 17.0 g. (0.20 mole) of piperidine and 21.6 g. (0.20 mole) of 3-chloropropionamide[7] in 100 ml. of methanol was refluxed for 4 hr., then filtered hot and evaporated to one-half of its original volume. Acetone was added and the mixture was allowed to crystallize. Filtration gave 30.5 g. (79%) of a nearly white solid, m.p. 193–196°. The analytical sample was prepared by several recrystallizations from a mixture of methanol and acetone, m.p. 197–198°. Its melting point was not depressed by admixture of the sample prepared by the hydrogenation of *N*-(2-carbamylethyl)pyridinium chloride. Infrared spectra of the two compounds were indistinguishable.

Anal. Calcd. for $C_8H_{17}ClN_2O$: C, 49.86; H, 8.89; Cl, 18.40; N, 14.54. Found: C, 50.32, 50.35; H, 8.85, 8.87; Cl, 18.34, 18.37; N, 14.85, 14.65.

Reaction of N-(2-carbamylethyl)piperidinium chloride with potassium carbonate. A solution of 9.35 g. (0.0485 mole) of the piperidinium compound III and 6.9 g. (0.05 mole) of potassium carbonate in a mixture of 200 ml. of methanol and 30 ml. of water was allowed to stand overnight. The solvent was evaporated *in vacuo* and the residue was dried by azeotropic distillation with benzene. It was then dissolved in ethyl acetate, filtered from inorganic salts, and evaporated to obtain a straw-colored oil which crystallized on standing. Recrystallization from a mixture of ether and hexane gave 6.5 g. (86%) of nearly white, highly hygroscopic plates, m.p. 63–68°, dissolving in water to give a strongly alkaline solution. Several recrystallizations from the same solvent gave an analytical sample, m.p. 80–81°.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.94. Found: C, 61.89, 61.61; H, 10.15, 9.99; N, 17.63, 17.60.

Preparation of 3-N-piperidylpropionamide (V). A solution of 14.2 g. (0.20 mole) of acrylamide in 50 ml. of 1,2-dimethoxyethane was added dropwise to a stirred solution of 17.0 g. (0.20 mole) of piperidine in 50 ml. of the same solvent. After stirring at room temperature for 3 hr. the solution was refluxed for the same period of time. Evaporation of the solvent *in vacuo* gave a straw-colored solid which was recrystallized from a mixture of ether and hexane to give 22.0 g. (70.5%) of a nearly white hygroscopic solid, m.p. 77–78°. The analytical sample was prepared by several recrystallizations from ether containing a small amount of methanol and hexane, m.p. 80–81°. Its melting point was undepressed on admixture of the sample prepared by treat-

(12) H. Henecka and P. Kurtz in *Methoden d. org. Chemie (Houben-Weyl)*, E. Müller, ed., Georg Thieme Verlag, Stuttgart, 1952, Vol. VIII, p. 663.

ment of III with potassium carbonate and the infrared spectra of the two compounds were identical.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.94. Found: C, 61.51, 61.34; H, 10.00, 10.19; N, 17.62, 17.59.

Acknowledgment. The author expresses his appreciation to Mr. R. F. Cornuet for a very able technical assistance, to Drs. C. L. Parris and W.-H. Chang for stimulating discussions and suggestions, to Drs. H. L. Gerhart, S. W. Gloyer, and R. M. Christenson for continued interest and encouragement, and to Professor C. D. Hurd for reading the manuscript.

SPRINGDALE, PA.

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

The Synthesis of Some Derivatives of Methioprim and Related Pyrimidines[1,2]

J. GRAHAM NAIRN[3-5] AND HOWARD TIECKELMANN

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Methioprim (2-methylthio-4-amino-5-hydroxymethylpyrimidine) was used for the preparation of several 2-substituted 4-amino-5-hydroxymethylpyrimidines. The conversions were conveniently accomplished by oxidation of the acetate of methioprim to 2-methanesulfonyl-4-amino-5-acetoxymethylpyrimidine which was subsequently treated with ammonia or amines to give the 2-substituted pyrimidines. The preparation of several esters and amides of methioprim and several sulfones of related pyrimidines are also described.

Interest in 2-methyl-4-amino-5-hydroxymethylpyrimidine (toxopyrimidine), 5-hydroxymethylcytosine, and 2-methylthio-4-amino-5-hydroxymethylpyrimidine (I, methioprim)[2] has led to the synthesis of analogs of these substances in several laboratories. Emphasis has been centered on 2-substituted-4-amino-5-hydroxymethylpyrimidines, some of which have been used as intermediates in the synthesis of thiamin analogs. Usually these 5-hydroxymethylpyrimidines are prepared by reduction of the corresponding 5-carbethoxypyrimidines with lithium aluminum hydride[2,6] although other routes have been useful. For example, 5-hydroxymethyluracil and related compounds have been prepared by the addition of formaldehyde to the pyrimidones.[7]

The discovery by Guthrie[8] of the unusual antimetabolite activity of I has led to a search for related, more potent compounds for experimental cancer chemotherapy. 2-Trifluoromethyl-, 2-methylthio-4-arylamino-5-carbethoxy-, and 2-methylthio-4-arylamino-5-hydroxymethylpyrimidines have been prepared.[6c,9a,b,c]

The present report deals mainly with the synthesis of derivatives from I. The availability of this compound[10] has made it an attractive intermediate for the synthesis of other 2-substituted-4-amino-5-hydroxymethylpyrimidines. The presence of the 5-hydroxymethyl group in the starting material avoids its repeated formation. In addition, the presence of the 2-methylthio group suggested facile substitution at this position. Sprague and Johnson[11] have shown that the oxidation of 2-alkylthiopyrimidines to 2-alkanesulfonylpyrimidines followed by amination or hydrolysis is a convenient route to 2-aminopyrimidines, 2-alkoxypyrimidines, and 2-pyrimidones. Chlorine water was used as the oxidizing agent. This method is often effective in cases where direct substitution of amino for alkylthio is difficult. However, failures have been noted.[12]

We were unable to substitute amino- or alkylamino- for methylthio- in I. Furthermore, it was not possible to isolate 2-methanesulfonyl-4-amino-5-hydroxymethylpyrimidine (V) from a reaction mixture of I and chlorine water. When the hydroxyl group was protected by acetylation (II), the sulfone (III) could be prepared by oxidation with chlorine. This sulfone was readily converted to V, 2,4-

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(2) For leading references see T. Okuda and C. C. Price, *J. Org. Chem.*, **23**, 1738 (1958).

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