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SUBSTITUTED UREAS

by

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ABSTRACT

Nitrosomethylurea in aqueous medium decomposes on heating to methanol, nitrogen and cyanic or isocyanic acid. Primary amines present during the decomposition react with cyanic acid to form substituted ureas, readily isolated in high purity and good yield.

THEORY

Numerous methods for the preparation of mono and di-substituted ureas are reported in the literature.(1-20) Few of these methods result in products simply obtained in high purity. It is the purpose of this paper to introduce a synthesis for substituted ureas whereby it is possible to produce the ureas in good yield and in a highly purified form without extensive recrystallization.

The mono-N-substituted urea derivatives wherein the substituted group is alkyl, aryl or heterocyclic have been prepared most readily by the following procedures.

i. The reaction between the hydrochloride salt of a primary amine and potassium cyanate.

$$RNH_2.HCl+KOCN \longrightarrow RNHCONH_2 + KCl \quad (1)$$

This is a very convenient method but it is extremely difficult to isolate the highly water soluble substituted ureas from the contaminating inorganic salts.

ii. Alkyl isocyanates are reacted with ammonia to give alkyl ureas.

$$R-N=C=O+NH_3 \longrightarrow RNHCO-NH_2 \quad (2)$$

This reaction is highly specific but not too widely used due to the inaccessibility of the isocyanates.

iii. The reaction of chloroformamide with a primary amine causes the formation of alkyl urea.

$R\text{-}NH_2 + Cl\text{-}CONH_2 \longrightarrow RNHCONH_2.HCl$ (3)

This reaction is very widely employed for the production of the hydrochloride salt; but it proves difficult to isolate the urea in a pure form free of contaminating salts.

iv. A more recent development in the preparation of substituted ureas is the method devised by Davis and Blanchard.(4) They heat nitrourea with the amine in an aqueous alcoholic solution, then isolate the urea by evaporating to dryness. Buck and Ferry (5) later improved upon this method by using 95% alcohol as their reaction medium, distilling to dryness and then recrystallizing from a suitable solvent.

v. J. Haager (6) in the "Behavior of Nitrosomonoarylcarbamide Towards Amines and Phenols", reported the synthesis of several aryl carbamides by reacting nitrosophenylcarbamide with the arylamine in an aqueous medium. Method of isolation and percentage of yield were not given.

vi. A paper has appeared since the start of the present work which substantiates this report. Boivin (7) expressed the belief that upon heating nitrosomethylurea in an aqueous medium, decomposition took place to form methanol, nitrogen and the isocyanic (or cyanic) acid, which reacted with the amine present to give the substituted urea. He substantiated this claim by an analysis of the boiling mixture, and found it to yield quantitative amounts of methanol, nitrogen and cyanic acid. He also reported the synthesis of several substituted ureas from primary and secondary aliphatic and aromatic monoamines.

In essence, the same principles involved in the above states reactions are employed in this study with the difference that the reaction is simple, easy to manipulate, requires no special equipment, and the product is easily isolated.

Nitrosomethylurea $H_2N.CON(NO)CH_3$ is a light yellow crystalline compound, insoluble in cold water and melts with decomposition above 120° C. It is comparatively stable at room temperature if kept damp with very dilute acetic acid. If allowed to dry out, it may decompose spontaneously with extreme violence, giving off obnoxious fumes.

It is made by dissolving methyl urea in dilute sulfuric acid, chilling to 0° C. and adding cold sodium nitrite solution. The crystals of nitrosomethylurea form and are easily separated by filtration.(8)

On hydrolysis with an alkali, nitrosomethylurea breaks down to diazomethane and the cyanate salt of the alkali.

$$H_2N.CON(NO).CH_3+KOH \longrightarrow CH_2N_2+KOCN+H_2O$$

An attempt was made to eliminate the use of caustic and to devise a method by which diazomethane could be generated at a controlled rate, through the use of an amine. Upon attempting this modification a highly exothermic reaction took place, with heavy foaming and rapid evolution of gas. Upon vacuum distillation of the reaction mixture, a white crystalline residue was isolated. A careful analysis of the residual crystals indicated that the substituted urea of the amine employed had been formed. Several more simple experiments employing the more readily available amines showed this to be the general case.

The supposition was that the amine reacted to convert the aqueous nitrosomethylurea mixture to methyl alcohol, nitrogen and isocyanic acid. The isocyanic acid then reacted with the amine to form the substituted urea.

$$CH_3NH(NO)CONH_2+RNH_2 \xrightarrow{H_2O} CH_3OH+N_2+HN=C=O$$

$$HN=C=O+RNH_2 \longrightarrow RNHCONH_2$$

Several of the ureas were synthesized without external heating, to cause previous decomposition of the nitrosomethylurea. Yields by this method were comparable to those isolated from the method of heating the aqueous solution before addition of the amine.

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TABLE I

AMINE	M.P.°C	B.P.°C Specifications* (Lit.)	UREA DERIVATIVE
Water Soluble Amines			
Methylamine (40% aq.)	-	-	Methylurea
n-Butylamine	-	74-79 (76-78)	n-Butylurea
Benzylamine	-	180-7 (185)	Benzylurea
Aniline	-	179-86 (184.4)	Phenylurea
Morpholine	-	120-32 (128.6)	Morpholine-carboxamide
Piperidine	-	103-10 (106.3)	Piperidine carboxamide
Furfurylamine	-	143-46 (144-6)	Furfurylurea
Cyclohexylamine	-	129-38 (134)	Cyclohexylurea
Ethylenediamine	-	116-19 (117.2)	Ethylenediurea
Propylenediamine	-	112-22 (119.7)	Propylenediurea
para-Phenylenediamine	138-41 (139.7)	(267)	para-Phenylenediurea

*B.P. specified for amines by supplier.

TABLE II

AMINE	M.P. °C	B.P. °C Specification* (Lit.)	UREA DERIVATIVE
Water Insoluble Amines			
n-Octadecylamine	Tech.	-	n-Octadecylurea
ortho-Aminobenzoic acid	141-146 (144-146)	-	ortho-Ureabenzoic Acid
para-Aminobenzoic acid	184-188 (186-187)	-	para-Ureabenzoic Acid
Ethyl-n-Butylamine	-	Tech.	Unable to isolate compound.
di-n-Butylamine	-	157-61 (159.8)	Unable to isolate compound.
2-Ethylhexylamine	-	165-68 (168.5-9.5)	2-Ethylhexylurea

*B.P. specified for amines by supplier.

TABLE III

UREA DERIVATIVE	M.P. °C Found	 Lit.	% Nitrogen Found	 Calc.	YIELD	REMARKS
Water Soluble Amines - Method 1.						
Methylurea	101-2	101-2	38.01	37.84	32-40%	Fine needles from methanol ether.
n-Butylurea	94-5	96	24.82	24.14	37-45%	Fine needles from benzene.
Benzylurea	147-9	147-8	18.83	18.66	65-70%	Large needles from water.
Phenylurea	147-8d	147d	20.60	20.58	70-75%	Large needles from water.
Morpholine-carboxamide	110-2	110-3	21.65	21.54	70-75%	Large platelets from ether.
Piperidine carboxamide	106-8	105-9	18.48*	21.87	35-40%	Large needles from ether chloroform.

*% Nitrogen is low. Probably due to a mole of water of crystallization. Calculating on this assumption % Nitrogen is 19.2.

(continued on next page)

TABLE III (continued)

UREA DERIVATIVE	M.P. °C		% Nitrogen		YIELD	REMARKS
	Found	Lit.	Found	Calc.		
Water Soluble Amines - Method 1.						
Furfurylurea	108-10	-	20.51	20.00	95+%	Large needles from water.
Cyclohexylurea	189-90	192-4	20.45	19.71	60-65%	Heavy granules from water.
Ethylenediurea	190-2	191-2	38.74	38.40	90-95%	Large crystals from water.
Propylenediurea	181-5	-	34.50	35.00	78-80%	Large crystals from methanol ether.
para-Phenylene-diurea	Chars above 340°	Chars	29.20	28.90	30-35%	Fine brown powder from water.

TABLE IV

UREA DERIVATIVE	M.P.°C Found	M.P.°C Lit.	% Nitrogen Found	% Nitrogen Calc.	YIELD	REMARKS
Water Insoluble Amines - Method 2						
n-Octadecylurea	110-3	111.5	9.65	9.47	55-60%	Large needles from chloroform.
Phenylurea-ortho-Carboxylic Acid	Unable to isolate compound.					
Phenylurea-para-Carboxylic Acid	Chars 300°C	-	16.00	15.60	75-80%	Yellow-brown powder from methanol water.
Ethyl-n-Butyl-Urea	Unable to isolate compound.					
di-n-Butylurea	Unable to isolate compound.					
2-Ethylhexylurea	79-81	-	17.00	16.28	15-20%	Large needles from water.

TABLE V

UREA DERIVATIVE	M.P. °C		% Nitrogen		YIELD	REMARKS
	Found	Lit.	Found	Calc.		
Water Soluble Amines - No External Heating - Method 3						
Methylurea	98-100	101-2	38.2	37.84	40-46%	Fine needles from methanol ether.
Furfurylurea	106.4-8.6	-	19.94	20.00	60-65%	Large needles from water.
Cyclohexylurea	191-3	192-4	20.15	19.71	65-70%	Heavy granules from water.
Propylenediurea	183-5	-	34.65	35.00	45-50%	Large crystals from methanol ether.

TABLE VI

Benzylurea Method 4.

Mole Ratio of Nitromethylurea to Benzylamine.	M.P. °C		% Nitrogen		YIELD	REMARKS
	Found	Lit.	Found	Calc.		
1.0	147-9	147-8	18.74	18.66	75-80%	Large needles from water.
1.2	145-8	147-8	17.99	18.66	85-90%	Large needles from water.
1.5	142-5	147-8	18.23	18.66	90-95%	Large needles from water.
2.0	140-4	147-8	16.77	18.66	95-100%	Large needles from water.

REAGENTS

The amines used were of a commercial or technical grade obtained from regular chemical supply sources. They were used directly as received.

EXPERIMENTAL PROCEDURE

Preparation of Nitrosomethylurea:

The nitrosomethylurea was synthesized by the method described in "Organic Synthesis", Collective Volume II. Yields were from 65 - 70% of theory.

Synthesis of Urea Derivatives from Water Soluble Amines:

Method I.

0.1 M of nitrosomethylurea was mixed with 200 ml. of distilled water and warmed gently on a steam cone while being agitated at high speed. When the temperature reached 40° C, 0.1 M of the amine was added dropwise during a period of ten to fifteen minutes. The rate of addition was determined by the amount of frothing and foaming present. The clear solution was then heated vigorously for five minutes on a steam bath. One-half gram of carbon black was added to the hot solution, agitated five minutes and filtered.

The solution was then vacuum distilled, at the pressure of the water pump, to dryness and the residue was recrystallized from a suitable solvent. Recrystallization method employed was to mix the residue with a solvent or solvents, heat the mixture until the residue was completely dissolved and allow to stand until crystals formed. The crystals were then removed by filtration and dried in an oven at 60° C. Solvents used are listed for each compound in Table III.

Synthesis of Urea Derivatives from Amines Sparingly Soluble in Water:

Method 2.

0.1 M of nitrosomethylurea was mixed with 200 ml. of distilled water and warmed gently on a steam cone while being agitated at a high speed. When the temperature reached 40° C, a dioxane solution of the amine (0.1 M of amine dissolved in 100 ml. dioxane) was added dropwise. Very little frothing was encountered with the exception of octadecylurea. The solution was then warmed vigorously for fifteen minutes to boil off a large portion of the dioxane.

The solution was then vacuum distilled, at the pressure of the water pump, to dryness and the residue was recrystallized from a suitable solvent. Recrystallization method employed was to mix the residue with a solvent or solvents, heat the mixture until the residue was completely dissolved, decolorize with Darco and then let stand until crystals formed. The crystals were then removed by filtration and dried in oven at 60° C. Solvents used are listed for each compound in Table IV.

The exception to the above procedure was in the case of octadecylurea. Upon the addition of the dioxane solution of octadecylurea, heavy foaming took place forming a white cream-like precipitate which could not be filtered. To isolate the urea, the mixture was extracted with chloroform in a liquid, liquid extractor for eight hours. The chloroform was then dried over sodium sulfate, filtered and cooled to -10° C. Large white needle crystals formed after prolonged standing. The crystals were then removed by filtration and dried in the oven at 60° C.

Synthesis of Urea Derivatives from Water Soluble Amines: No External Heating.

Method 3.

0.1 M. of nitrosomethylurea was mixed with 50 ml. of distilled water. 0.1 M. of the amine was then added dropwise with gentle agitation and the temperature was allowed to rise by the heat of reaction. Temperatures normally varied from 18 - 70° C.

The solution was then vacuum distilled, at the pressure of the water pump, to dryness and the residue was recrystallized from a suitable solvent. Procedure for recrystallization is the same as that described in Method 1. Solvents used are listed for each compound in Table V.

Synthesis of Benzylurea:

Method 4.

Reaction procedure is same as that described in Method 3. The exception is that an attempt was made to increase the overall yield by varying the ratio of the nitrosomethylurea to the benzylamine. Benzylamine was selected because of ease of isolation of the urea derivative. Variations of 0.1 moles, 0.12 moles, 0.15 moles, and 0.2 moles of nitrosomethylurea to 0.1 moles of benzylamine were used. This led to a slight increase in the overall yield. The percentage of nitrogen remained relatively the same while the melting point dropped with the increase of nitrosomethylurea. Table VI.

APPARATUS

All apparatus used in obtaining experimental data for this report was of the general type found in the laboratory, such as beakers, mechanical stirrers, water pump, steam cone and Kjeldahl assay equipment. No special equipment was used or required.

ASSAY METHOD

The Kjeldahl method for the determination of nitrogen was employed in the analysis of the ureas. All assays were run in duplicate or triplicate.

All melting points between the range of 0° to 200° C. were taken in a triethylene glycol bath employing the proper Anschutz thermometer. All melting points above 200° C. were taken on an electrically heated melting point block.

Laboratory facilities were not available to permit the running of a complete carbon, hydrogen and oxygen analysis. The assumption that the compounds not found in literature checked are the desired compounds are based on the percentage of nitrogen and validity of the reaction as shown in other experiments where the specific constants were given.

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DISCUSSION

Before a satisfactory solution to this investigation could be reached, there were three basic problems that had to be decided upon:

1. Selection of the amines.
2. Devising method by which water soluble and water insoluble amines could be reacted.
3. Selection of solvent for recrystallizing urea derivatives.

1. Selection of amines were based on those more readily available and where the physical constants were easily found so as to check results.

2. Methods given in Experimental Procedure were decided upon after preliminary experimentation and a careful study of mechanism and results.

3. Selection of solvent for recrystallization was very complex because of the varied difference in solubilities of the different urea derivatives. All solvents used are listed in Tables III to VI.

SUMMARY

1. Nitrosomethylurea reacts readily with primary amines to form the corresponding substituted ureas.

2. This reaction is thought to be due to the decomposition of nitrosomethylurea to methanol, nitrogen and cyanic acid.

3. Since all products other than the substituted ureas are readily volatile, isolation and purification of the ureas is relatively simple. Yields of ureas range from twenty per cent to over ninety-five percent in individual cases.

4. Secondary amines also react with nitrosomethylurea, but pure products could not be isolated.

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