[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Reactions of Orthoesters with Ureas. A New Synthesis of Pyrimidines

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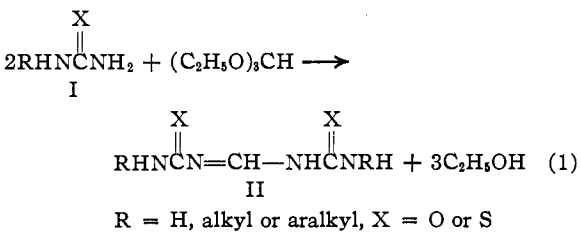
Ethyl orthoformate was allowed to react with urea and some of its derivatives to obtain N,N′-dicarbamylformamidines. The isolation of an ureidoacetal and its conversion to the N,N′-dicarbamylformamidine suggested a mechanism for this reaction. Alcoholysis of the urea resulting in the cleavage of the carbonyl–nitrogen bond was observed as a side reaction. Active methylene compounds were added to the nitrogen–carbon double bond of the N,N′-dicarbamylformamidines to yield substituted ureidoethylenes. The rate of this addition was dependent upon the nature of the activating groups of the methylene compound. The convenient preparation of these substituted ureidoethylenes by the direct interaction of ethyl orthoformate, the urea and a methylene compound and their further cyclization made possible a new synthesis of pyrimidines.

Alkyl orthoesters react with ammonia and some of its derivatives with the elimination of an alcohol and the formation of a nitrogen–carbon linkage. This is particularly exemplified by the action of orthoesters upon amines and diamines to yield linear and cyclic amidines, respectively.[1] In the few reported reactions of orthoesters with amides it has been shown that the formation of a stable nitrogen–carbon bond may not always occur. Acetamide and ethyl orthoformate react at 180° to give N,N′-diacetylformamidine,[2] while under similar conditions methyl trimethoxyacetate causes the cleavage of the carbonyl–nitrogen bond.[3]

The investigation of the condensations of ethyl orthoformate with urea and its derivatives was undertaken on the assumption that these reactions would take place in a manner analogous to the formation of amidines rather than result in a cleavage of the urea. A second and equally important purpose was the development of a new synthesis of pyrimidines.

Ethyl orthoformate reacted with urea, N-alkyl ureas, aralkyl ureas and alkyl thioureas with the formation of N,N′-dicarbamylformamidines (II) as shown in equation 1.

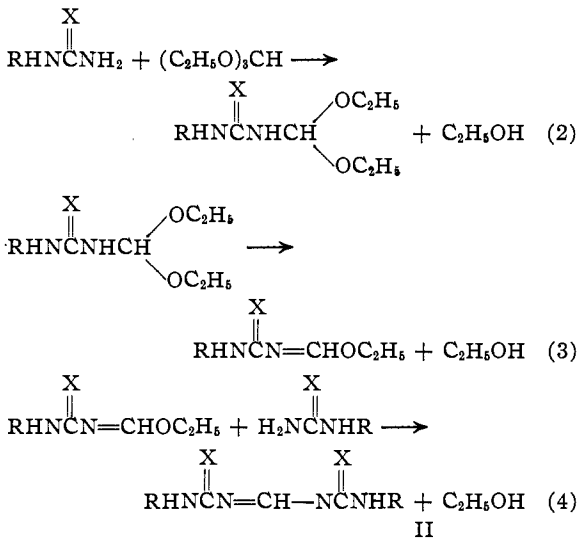


$$2\mathrm{RHNC(X)NH_2}\ (\mathrm{I}) + (\mathrm{C_2H_5O})_3\mathrm{CH} \longrightarrow \mathrm{RHNC(X)N{=}CH{-}NHC(X)NRH}\ (\mathrm{II}) + 3\mathrm{C_2H_5OH} \quad (1)$$

R = H, alkyl or aralkyl, X = O or S

Urea, alkyl ureas and aralkyl ureas (I, R = H, alkyl or aralkyl, X = O) gave high-melting insoluble white crystalline solids. Thioureas (I, R = alkyl, X = S) reacted with the evolution of ethanol but yielded oils. Acyl ureas (I, R = CH_3CO, X = O) and N,N′-dialkyl ureas failed to react at 145–150°. The action of the orthoester upon aromatic ureas (I, R = aryl, X = O) caused the cleavage of the nitrogen–carbon bond of the urea. Since the desired N,N′-dicarbamylformamidine was not obtained as the major product the description of this unexpected cleavage has been reserved for a separate presentation.

The reaction of cyclohexylurea and ethyl orthoformate gave N,N′-bis-(cyclohexylcarbamyl)-formamidine (II, R = cyclohexyl, X = O) in 82.3% yield, ethyl N-cyclohexylcarbamate, $C_6H_{11}NHCO_2C_2H_5$, in 6.2% yield and N-cyclohexylureidoacetal, $C_6H_{11}NHCONHCH(OC_2H_5)_2$, in 2.3% yield. The presence of the ureidoacetal (III) in the reaction suggested the mechanism in the formation of N,N′-dicarbamylformamidines might be

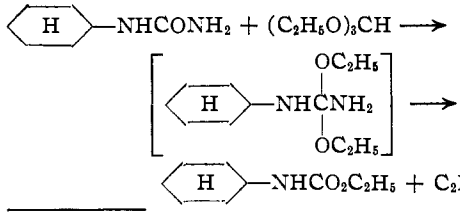


$$\mathrm{RHNC(X)NH_2} + (\mathrm{C_2H_5O})_3\mathrm{CH} \longrightarrow \mathrm{RHNC(X)NHCH(OC_2H_5)_2} + \mathrm{C_2H_5OH} \quad (2)$$

$$\mathrm{RHNC(X)NHCH(OC_2H_5)_2} \longrightarrow \mathrm{RHNC(X){=}CHOC_2H_5} + \mathrm{C_2H_5OH} \quad (3)$$

$$\mathrm{RHNC(X){=}CHOC_2H_5} + \mathrm{H_2NC(X)NHR} \longrightarrow \mathrm{RHNC(X){=}CH{-}NC(X)NHR}\ (\mathrm{II}) + \mathrm{C_2H_5OH} \quad (4)$$

The possibility that a ureidoacetal might be a precursor of the dicarbamylformamidines (II) was established when N-cyclohexylureidoacetal was heated in a solvent with cyclohexylurea to obtain N,N′-bis-(cyclohexylcarbamyl)-formamidine. The intermediate IV was not isolated but its transient existence is indicated by the results of similar reactions,[4] *i.e.*, the monoethoxy compounds X-$C_6H_4N{=}CHOC_2H_5$ (X = H, *p*-Cl and *o*-Cl) were found as intermediates in the formation of amidines from aryl amines and ethyl orthoformate.[5] It is suggested that ethyl N-cyclohexylcarbamate was



$$\mathrm{C_6H_5NHCONH_2} + (\mathrm{C_2H_5O})_3\mathrm{CH} \longrightarrow \mathrm{C_6H_5NHCH(OC_2H_5)_2NH_2} \longrightarrow \mathrm{C_6H_5NHCO_2C_2H_5} + \mathrm{C_2H_5NH_2} \quad (5)$$

(1) H. W. Post, "The Chemistry of Aliphatic Orthoesters," Am. Chem. Soc. Monograph Series 92, Reinhold Publishing Corp., New York, N. Y., Chap. 5.

(2) H. Wichelhaus, *Ber.*, **3**, 2 (1870).

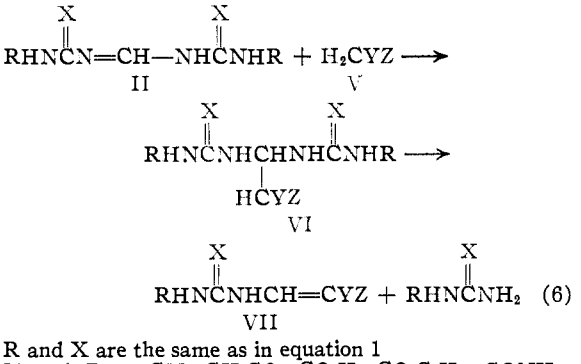
(3) R. Anschütz and J. Stiepel, *Ann.*, **306**, 8 (1909).

(4) Monoethoxy compounds corresponding to IV have been isolated from the reactions of other orthoesters with ureas. This work is currently in process and is to be presented at a later date.

(5) E. B. Knott and R. A. Jeffreys, *J. Org. Chem.*, **14**, 879 (1949).

obtained as the result of an attack by the ortho-ester upon the carbonyl group of cyclohexylurea with subsequent cleavage of the carbonyl–nitrogen bond.

Reaction of active methylene compounds with the N,N′-dicarbamylformamidines, equation 6, proceeded in a similar manner to that demonstrated with N,N′-diarylamidines.[6,7]

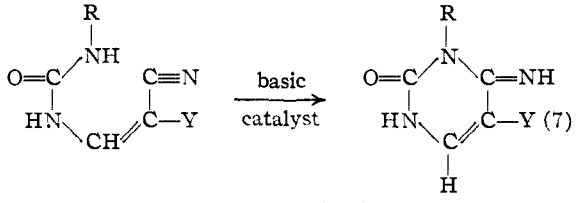


R and X are the same as in equation 1
Y and Z = CN. CH_3CO. CO_2H. $CO_2C_2H_5$. $CONH_2$ or $COCO_2C_2H_5$

The methylene compound (V) underwent addition to the nitrogen–carbon double bond of the amidine (II) presumably producing an unstable adduct (VI). By loss of a molecule of the original urea the substituted ureidoethylene (VII) could have resulted. The rate of the addition was shown to be dependent upon the activating groups Y and Z. A comparison was made of the time required for complete utilization of N,N′-bis-(cyclohexylcarbamyl)-formamidine (II, R = cyclohexyl, X = O) when allowed to react under similar conditions with various methylene compounds. A suspension of N,N′-bis-(cyclohexylcarbamyl)-formamidine in ethanol was unchanged after several days of heating at refluxing temperature. However, when the stirred suspension was heated at 70° with one of the active methylene compounds (V), the above formamidine disappeared as the addition proceeded. The time required for complete disappearance of the formamidine was considered to be a measure of the rate of addition of the methylene compound to the formamidine. The order of the activating groups Y and Z according to their effect upon increasing the rate of the addition was $CO_2H > CN > COCH_3 \gg CO_2C_2H_5$ (Table II). Malonic acid reacted within 3–4 minutes while malonic ester required approximately 60 hours. The great difference noted between the activating influences of a carboxyl group and a carbethoxy group could not be accounted for on the basis of increased solubility of the formamidine as a result of the presence of an acid group. When both malonic acid and diethyl malonate were present in the reaction mixture, the product isolated in 75.6% yield was that resulting from the reaction with malonic acid. None of the product from malonic ester could be found.

Preparation of the ureidoethylenes (VII) was conveniently accomplished without isolation of the intermediate dicarbamylformamidines (II). Equal molar quantities of the urea (I) and the active methylene compound (V) were added to an excess of ethyl orthoformate and were either refluxed for 1–12 hours or allowed to stand at room temperature for one day. When malononitrile was used as the methylene compound the reaction was complete after refluxing for 1–2 hours. A longer period of heating, 8–12 hours, was required for ethyl acetoacetate, ethyl cyanoacetate, cyanoacetamide and acetylacetone. Diethyl malonate gave poor yields with N-alkyl ureas but in contrast readily reacted with ethyl orthoformate and urea to yield ureidomethylenemalonate (VII, R = H, X = O, Y = Z = $CO_2C_2H_5$). Diethyl oxalacetate and malonic acid reacted at room temperature to yield the ureidomethyleneoxalacetate and the ureidomethylenemalonic acids, respectively. Decarboxylation occurred when malonic acid, the urea and ethyl orthoformate were heated together, and the products were ureidoacrylic acids.

The ureidoethylenes (VII) described in this paper have general utility in the synthesis of many new pyrimidines and make possible the convenient preparation of some known compounds previously prepared by more laborious methods. In an earlier report[8] the cyclization of the alkyl ureidomethylenemalonates (VII, R = alkyl, X = O, Y = Z = $CO_2C_2H_5$) to 5-carbethoxyuracils was described. Bergmann and Johnson[9] have shown that Claisen's[10] ethyl ureidomethyleneacetoacetate (VII, R = H, X = O, Y = $COCH_3$ and Z = $CO_2C_2H_5$) could be converted to either 5-acetyluracil or 2-hydroxy-4-methyl-5-carbethoxypyrimidine depending upon the ring-closing conditions. Further utility of these ureidoethylenes (VII) and extension of this method to obtain six-membered heterocyclic rings is presented here by the cyclization of N-*n*-amylureidomethylenemalononitrile (VII, R = *n*-amyl, X = O, Y = Z = CN) and ethyl ureidomethylenecyanoacetate (VII, R = H, X = O, Y = $CO_2C_2H_5$ and Z = CN) to yield, respectively, 3-*n*-amyl-5-cyanocytosine and 5-carbethoxycytosine, equation 7.



R = H and Y = $CO_2C_2H_5$
R = *n*-amyl and Y = CN

A number of new and interesting pyrimidines have been prepared by the methods described above and others are being investigated.

Acknowledgment.—The author is grateful to W. L. Brown, H. L. Hunter, W. J. Schenck and G. M. Maciak for the microanalyses reported here.

Experimental

Synthesis of N,N′-Dicarbamylformamidines.—Urea, N-alkyl ureas or N-aralkyl ureas were separately added to an excess of ethyl orthoformate and the mixture refluxed for

(6) C. C. Price, N. J. Leonard and H. F. Herbrandson, THIS JOURNAL, **68**, 1251 (1946).
(7) H. R. Snyder and R. E. Jones, *ibid.*, **68**, 1253 (1946).
(8) C. W. Whitehead, *ibid.*, **74**, 4267 (1952).
(9) W. Bergmann and T. B. Johnson, *Ber.*, **66**, 1492 (1933).
(10) L. Claisen, *Ann.*, **297**, 33 (1897).

TABLE I

N,N'-DICARBAMYLFORMAMIDINES, RNHCON=CH—NHCONHR

R	Yield, %	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	70	206	$C_5H_{10}N_4O_2$					35.41	35.63
C_2H_5	94.6	186	$C_7H_{14}N_4O_2$	45.20	45.75	7.58	7.63		
$(CH_3)_3C$	51	191	$C_{11}H_{22}N_4O_2$					22.72	22.57
n-C_5H_{11}	95	197	$C_{13}H_{26}N_4O_2$	57.60	57.25	9.72	9.63		
$C_6H_5CH_2$	91	206	$C_{17}H_{18}N_4O_2$	65.90	65.56	5.85	6.06		
n-C_7H_{15}	67	194	$C_{17}H_{34}N_4O_2$					17.15	16.72
n-C_8H_{17}	61	183	$C_{19}H_{38}N_4O_2$	64.50	64.61	10.22	10.86		

10–12 hours. In each case the insoluble crystalline N,N'-dicarbamylformamidine separated from the solution. The solid was filtered off and purified by recrystallization. The high melting N,N'-dicarbamylformamidines are insoluble in alcohol, acetone, ether and benzene, moderately soluble in dimethylformamide and soluble in dilute acids. The preparation and purification of representative examples are given below. Other N,N'-dicarbamylformamidines prepared in a like manner are listed in Table I.

N,N'-Dicarbamylformamidine.—Urea (120 g. or 2.0 moles) was added to 300 ml. of ethyl orthoformate and the mixture heated at refluxing temperature for 10 hours. The reaction mixture was cooled and the N,N'-dicarbamylformamidine filtered off and washed with ether; yield 110 g. or 84.5%. An analytical sample was prepared by recrystallizing from a mixture of 90% dimethylformamide and 10% water; m.p. 234°. The product was soluble in water and insoluble in alcohol.

Anal. Calcd. for $C_3H_6N_4O_2$: C, 27.67; H, 4.65. Found: C, 27.59; H, 4.36.

N,N'-Bis-(cyclohexylcarbamyl)-formamidine.—Cyclohexylurea (100 g. or 0.7 mole) and an excess of ethyl orthoformate (250 ml.) were mixed and heated at refluxing temperature for 12 hours. The N,N'-bis-(cyclohexylcarbamyl)-formamidine separated and was filtered from the hot solution and washed with ether; yield 85 g. or 82.3%, m.p. 205°. When recrystallized from dimethylformamide the product melted at 207°.

Anal. Calcd. for $C_{15}H_{26}N_4O_2$: C, 61.27; H, 8.92. Found: C, 60.96; H, 8.89.

N-Cyclohexylureidoacetal.—The warm filtrate obtained from the preparation of N,N'-bis-(cyclohexylcarbamyl)-formamidine was concentrated under reduced pressure to one-tenth its original volume and cooled in ice. N-Cyclohexylureidoacetal separated and when recrystallized from ethyl acetate gave a melting point of 145°, yield 4 g. or 2.3%.

Anal. Calcd. for $C_{12}H_{24}N_2O_4$: C, 59.05; H, 9.94. Found: C, 59.01; H, 10.14.

Ethyl N-Cyclohexylcarbamate.—The filtrate from N-cyclohexylureidoacetal was evaporated to obtain an oil. This oil was distilled without decomposition through a small Claisen head; b.p. 137° (1 mm.), yield 7 g. or 6.2%. The distilled oil solidified and was recrystallized from benzene–petroleum ether mixture and from petroleum ether alone, m.p. 52°. An analytical sample was prepared by recrystallizing several times from dilute alcohol, m.p. 55–57°. Elemental analysis was made to determine its empirical formula and after its identity was known the melting point was found identical to that reported.[11]

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.15; H, 9.94; N, 8.20. Found: C, 63.15; H, 9.92; N, 7.98.

N,N'-Bis-(cyclohexylcarbamyl)-formamidine from Cyclohexylureidoacetal.—Cyclohexylureidoacetal (70 mg. or 0.0029 mole) and cyclohexylurea (40 mg. or 0.0029 mole) were added to 2 ml. of dimethylformamide and refluxed for 1 hour. The dimethylformamide was concentrated under reduced pressure and allowed to cool. N,N'-Bis-(cyclohexylcarbamyl)-formamidine crystallized from solution, m.p. 207°. When mixed with a sample prepared by the previous method the melting point was not depressed. The yield was 20 mg. or 24.4%.

Attempted Reaction of Ethyl Orthoformate with N-Acetylurea and N,N'-Dialkylureas.—N-Acetylurea, N,N'-dibutylurea and N,N'-dibenzylurea were separately refluxed with an excess of ethyl orthoformate for 24 hours. The ethyl orthoformate was removed by reduced pressure distillation. The resulting solids were recrystallized from ethyl acetate or alcohol. In each case the original urea was recovered unchanged.

Addition of Active Methylene Compounds to N,N'-Dicarbamylformamidines

N-Ethylureidomethylenemalononitrile.—N,N'-Bis-(ethylcarbamyl)-formamidine (9.3 g. or 0.05 mole) and malononitrile (3.9 g. or 0.055 mole) were added to 200 ml. of ethylene dichloride and heated at refluxing temperature for two hours. The solution was concentrated to a volume of 50 ml. Sufficient petroleum ether was added to cause complete precipitation of the solid products. The solid residue was dissolved in 75 ml. of warm alcohol. Water was added to incipient turbidity and N-ethylureidomethylenemalononitrile crystallized as the solution cooled; yield 5.3 g. or 62.5%, m.p. 167°.

Anal. Calcd. for $C_7H_8N_4O$: C, 51.10; H, 4.90; N, 34.10. Found: C, 50.89; H, 5.10; N, 33.86.

The above alcohol–water filtrate was clarified with carbon, filtered and evaporated to dryness. The residue was recrystallized from a mixture of ethyl acetate and petroleum ether to yield 2.7 g. or 61.5% of N-ethylurea, m.p. 92°.

N-Benzylureidomethylenemalonic Acid.—N,N'-Bis-(benzylcarbamyl)-formamidine (25 g. or 0.081 mole) and malonic acid (7.15 g. or 0.081 mole) were added to 250 ml. of ethyl alcohol and stirred at room temperature for 4 hours. The alcohol was removed under reduced pressure. The residue was extracted by sodium bicarbonate solution. The insoluble benzylurea was filtered off and recrystallized from ethyl alcohol–water mixture, yield 8 g. or 66%. The clear sodium bicarbonate filtrate was acidified with dilute hydrochloric acid. The precipitated N-benzylureidomethylenemalonic acid was filtered off and dried, yield 11 g. or 51%, m.p. 200° (dec.).

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.58. Found: C, 54.54; H, 4.66.

Effect of Activating Groups upon the Addition of Methylene Compounds to Dicarbamylformamidines.—N,N'-Bis-(cyclohexylcarbamyl)-formamidine (14.7 g. or 0.05 mole) was added to 100 ml. of absolute ethanol. The suspension was stirred mechanically at a constant speed and heated to 70°. The methylene compound (0.1 mole) was added and the time necessary for the suspended material to react and completely dissolve was recorded. The resulting solution was evaporated under reduced pressure and the residue extracted with ether. The undissolved cyclohexylurea was removed by filtration, recrystallized from ethyl acetate, collected, dried and weighed. The ether-soluble ureidoethylene was caused to crystallize by the addition of petroleum ether. This product was recrystallized from a mixture of ether and petroleum ether, collected, dried and weighed. The product from malonic acid was separated from cyclohexylurea by extraction with sodium bicarbonate solution. The N-cyclohexylureidomalonic acid was then recovered by acidification of the bicarbonate filtrate. The products obtained were identified by comparison of their melting points with the expected compound listed in Table III. The results of this series of reactions are listed in Table II. The N,N'-bis-(cyclohexylcarbamyl)-formamidine by itself was unchanged after several days of refluxing in alcohol suspension.

A similar experiment was carried out designed to determine whether the rapid reaction between malonic acid and N,N'-bis-(cyclohexylcarbamyl)-formamidine was a result of

(11) M. Baker, L. Hunter and N. G. Reynolds, *J. Chem. Soc.*, 874 (1948).

TABLE II

EFFECT OF ACTIVATING GROUPS Y AND Z OF H_2CYZ UPON THE ADDITION TO N,N'-BIS-(CYCLOHEXYLCARBAMYL)-FORMAMIDINE

Y	Z	Time required for completion	Yield, % cyclohexylurea	Product N-cyclohexylureidomethylene-	Yield, %
CN	CN	15 min.	95	Malononitrile	52
CO_2H	CO_2H	3–4 min.	95	Malonic acid	64.7
CH_3CO	$CO_2C_2H_5$	4 hr.	87	Acetoacetate	41
CN	$CO_2C_2H_5$	30 min.	95	Cyanoacetic ester	65
$CO_2C_2H_5$	$CO_2C_2H_5$	60 hr.	80	Malonic ester	24

Ethyl Ureidomethylenecyanoacetate.—Urea (180 g. or 3.0 moles), ethyl orthoformate (500 g. or 3.38 moles) and ethyl cyanoacetate (372 g. or 3.3 moles) were mixed and heated at refluxing temperature for 8 hours. The mixture was cooled and the solid product that separated was filtered off and washed with ether; yield 444 g. or 69%. An analytical sample was prepared by recrystallization from ethyl acetate; m.p. 215°.

Anal. Calcd. for $C_7H_9N_3O_3$: C, 45.95; H, 4.96. Found: C, 45.59; H, 5.14.

Diethyl Ureidomethylenemalonate.—Urea (60 g. or 1.0 mole), ethyl orthoformate (148 g. or 1.0 mole) and diethylmalonate (160 g. or 1.0 mole) were mixed and refluxed for 10 hours. The alcohol was removed under reduced pressure. The solid residue was dissolved in a mixture of equal parts of alcohol and ethyl acetate. The hot solution was filtered and allowed to cool. Diethyl ureidomethylenemalonate,[12] m.p. 207°, was obtained in 40% yield.

N-*n*-Hexylureidomethylenemalononitrile.—N-*n*-Hexylurea (144 g. or 1.0 mole), ethyl orthoformate (158 g. or 1.1 mole) and malononitrile (72 g. or 1.1 mole) were refluxed together for 2 hours. The volatile substances were removed under reduced pressure leaving a solid residue. This latter was dissolved in hot ethanol, clarified with charcoal and filtered. Water was added to the hot filtrate to incipient turbidity. Upon cooling *n*-hexylureidomethylenemalononitrile crystallized from solution; yield 156 g. or 71%, m.p. 142°.

TABLE III

UREIDOETHYLENES, $RNHCNHCH{=}C(Y)Z$

R	Y	Z	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	CN	CN	71	>250 dec.	$C_6H_6N_4O$	47.95	4.03	37.32	47.84	4.19	37.02
H	CN	CO_2CH_3	65	215	$C_6H_7N_3O_3$	42.55	4.16		42.30	5.85	
H	$COCH_3$	$COCH_3$	56	201–203	$C_7H_{10}N_2O_3$			16.59			16.21
$(CH_3)_2CH$	CN	CN	97.5	210–215	$C_8H_{10}N_4O$			31.43			31.10
C_3H_7	CN	CN	86	160	$C_8H_{10}N_4O$	53.80	5.66		53.71	5.73	
$(CH_3)_2CH$	CN	CO_2H	90	189 dec.	$C_6H_{11}N_3O_3$	48.60	5.63		48.59	5.85	
$HO(CH_2)_2$	CN	CO_2CH_3	23	159–160	$C_8H_{11}N_3O_4$	45.10	5.22		45.31	5.39	
H	$COCH_3$	$CO_2C_2H_5$	63	194–195	$C_8H_{12}N_2O_4$	48.05	6.04		47.91	6.01	
n-C_4H_9	CN	CN	80	139–141	$C_9H_{12}N_4O$			29.10			28.48
$(CH_3)_3C$	CN	CN	83.5	215–220 dec.	$C_9H_{12}N_4O$	56.25	6.30		56.25	6.60	
$CH_3CH_2(CH_2OH)CH$	CN	CN	68	201	$C_9H_{12}N_4O_2$			26.82			27.09
C_2H_5	CN	$CO_2C_2H_5$	43	156–157	$C_9H_{13}N_3O_3$	51.20	6.21	19.92	50.97	6.27	20.21
$(CH_3)_2CH$	CN	CO_2CH_3	91	159	$C_9H_{13}N_3O_3$			19.92			19.57
CH_3	$COCH_3$	$CO_2C_2H_5$	54	134–135	$C_9H_{14}N_2O_4$			13.10			12.82
n-C_5H_{11}	CN	CN	73	141–142	$C_{10}H_{14}N_4O$			27.16			27.14
$(CH_3)_2CH$	CN	$CO_2C_2H_5$	70	151–152	$C_{10}H_{15}N_3O_3$			18.66			18.88
Cyclohexyl	CN	CN	85.5	219 dec.	$C_{11}H_{14}N_4O$			25.65			25.55
Cyclohexyl	CN	$CONH_2$	70	242	$C_{11}H_{16}N_4O_2$	55.90	6.84		56.14	6.93	
n-C_4H_9	CN	$CO_2C_2H_5$	36	149	$C_{11}H_{17}N_3O_3$	55.25	7.16		55.29	7.34	
$(CH_3)_3C$	CN	$CO_2C_2H_5$	78	161	$C_{11}H_{17}N_3O_3$	55.25	7.16		55.69	7.51	
n-C_7H_{15}	CN	CN	90	130–132	$C_{12}H_{18}N_4O$	61.50	7.75		61.64	7.90	
$CH_3(CH_2)_4(CH_3)CH$	CN	CN	65	149	$C_{12}H_{18}N_4O$	61.50	7.75		61.12	7.84	
n-C_5H_{11}	CN	$CO_2C_2H_5$	67	95–100	$C_{12}H_{19}N_3O_3$			17.15			17.31
Cyclohexyl	CN	$CO_2C_2H_5$	72	156	$C_{13}H_{19}N_3O_3$	58.90	7.20	15.85	59.00	7.27	15.45
n-C_8H_{17}	CN	CN	82	95–96	$C_{13}H_{19}N_4O$	63.00	8.12	22.15	63.10	8.59	21.56
Cyclohexyl	$COCH_3$	$COCH_3$	70	149–150	$C_{13}H_{20}N_2O_3$	62.00	7.96	11.10	62.06	7.88	11.22
n-C_6H_{13}	CN	$CO_2C_2H_5$	72	129–130	$C_{13}H_{21}N_3O_3$	58.49	7.92		58.34	7.94	
n-C_7H_{15}	CN	CO_2CH_3	67	121	$C_{13}H_{21}N_3O_3$			15.72			15.29
n-C_7H_{15}	CN	$CO_2C_2H_5$	66	124–126	$C_{14}H_{23}N_3O_3$			14.92			14.54
n-C_8H_{17}	CN	CO_2CH_3	100	128	$C_{14}H_{23}N_3O_3$			14.92			15.21
$C_6H_5CH_2$	$COCH_3$	$CO_2C_2H_5$	74	134	$C_{15}H_{18}N_2O_4$			9.66			9.56
Cyclohexyl	$CO_2C_2H_5$	$CO_2C_2H_5$	50	92	$C_{15}H_{24}N_2O_5$	57.60	7.75		57.78	7.56	

a solubilizing effect of the acid group. Both malonic acid (0.10 mole) and diethyl malonate (0.10 mole) were added as described above to an alcoholic suspension of 29.4 g. or 0.1 mole of N,N'-bis-(cyclohexylcarbamyl)-formamidine. After 5 minutes at 70° the reaction was complete and the products were isolated, yielding N-cyclohexylureidomethylenemalonic acid, 12 g. or 75.6%, and cyclohexylurea, 15 g. or 91.7%. Diethyl N-cyclohexylureidomethylenemalonate could not be found among the products.

Direct Synthesis of Substituted Ureidoethylenes

The following descriptions are given to illustrate the synthetic methods. Other members of this series are listed in Table III.

(12) H. L. Wheeler, T. B. Johnson and C. O. Johns, *Am. Chem. J.*, **37**, 392 (1907).

Anal. Calcd. for $C_{11}H_{16}N_4O$: N, 25.43. Found: N, 25.68.

Ethyl N-*n*-Hexylthioureidomethylenecyanoacetate.—N-*n*-Hexylthiourea (16 g. or 0.1 mole), ethyl orthoformate (17 g. or 0.115 mole) and ethyl cyanoacetate (11.3 g. or 0.1 mole) were mixed together and heated to refluxing temperature for 30 minutes. The mixture was concentrated under reduced pressure to obtain the solid product. This was recrystallized from ethyl acetate; yield 11.5 g. or 41%, m.p. 152°.

Anal. Calcd. for $C_{13}H_{21}N_3O_2S$: S, 11.33. Found: S, 11.42.

N-Cyclohexylureidoacrylic Acid.—N-Cyclohexylurea (14.2 g. or 0.1 mole), ethyl orthoformate (20 g. or 0.135 mole) and malonic acid (10.4 g. or 0.1 mole) were mixed and heated at refluxing temperature for 2 hours. The solution was concentrated and the cyclohexylureidoacrylic acid allowed to crystallize; yield 16 g. or 75%, m.p. 182° (dec.).

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: N, 13.45. Found: N, 13.29.

N-Cyclohexylureidomethylenemalonic Acid.—Cyclohexylurea (14.2 g. or 0.1 mole) and malonic acid (10.4 g. or 0.1 mole) were added to 100 ml. of ethyl orthoformate and stirred mechanically. After 5 minutes the mixture became cool, the reactants dissolved and the product began separating from solution. The stirring was continued overnight. The solid was filtered off and washed white with ether; yield 23 g. or 92%. An analytical sample was prepared by reprecipitation from bicarbonate solution; m.p. 180° (dec.).

Anal. Calcd. for $C_{11}H_{16}N_2O_5$: N, 10.92. Found: N, 10.89.

Diethyl N-Cyclohexylureidomethyleneoxalacetate.—N-Cyclohexylurea (71 g. or 0.5 mole), ethyl orthoformate (74 g. or 0.5 mole) and freshly distilled diethyl oxalacetate (94.0 g. or 0.5 mole) were mixed and allowed to stand at room temperature. After 0.5 hour the reaction mixture had become completely solid. This was allowed to stand overnight and then dissolved in a minimum amount of warm alcohol. Water was added to the warm alcohol solution to incipient turbidity. Diethyl N-cyclohexylureidomethyleneoxalacetate crystallized as a beautiful white product; yield 137 g. or 88%, m.p. 127–128°.

Anal. Calcd. for $C_{16}H_{24}N_2O_6$: C, 56.45; H, 7.06. Found: C, 56.44; H, 7.11.

5-Carbethoxycytosine.—Sodium (46 g. or 2.0 g. atoms) was added to 750 ml. of absolute ethanol in a 2-l. flask fitted with a reflux condenser. After the sodium had completely reacted ethyl ureidomethylenecyanoacetate was added and the mixture agitated. A vigorous reaction occurred and the contents of the flask became solid. Ethanol (300 ml.) was added and the solid was broken into small lumps. The flask was heated under reflux for one-half hour. The alcohol was removed by filtration and the remaining solid dissolved in 8 l. of cool water. This solution was filtered and acidified with glacial acetic acid. The precipitated product was collected on a buchner funnel and sucked dry, washed with alcohol and then with ether, yield 176 g. or 96.3%. The 5-carbethoxycytosine decomposed slowly at 260–270°.[13]

3-*n*-Amyl-5-cyanocytosine.—N-*n*-Amylureidomethylenemalononitrile (41.2 g. or 0.2 mole) was added to 250 ml. of methanol. Sodium methylate (10.8 g. or 0.2 mole) was added and the mixture stirred until the solids were dissolved. The flask was stoppered and allowed to stand at room temperature. After 5 days the alcohol was removed and 500 ml. of cold water was added to dissolve the residue. The water solution was made neutral by the addition of dilute acetic acid. The precipitated solid was collected and recrystallized from ethanol; yield 29 g. or 71%, m.p. 209°. An analytical sample was prepared by repeated recrystallization from alcohol, m.p. 210°.

Anal. Calcd. for $C_{10}H_{14}N_4O$: C, 58.35; H, 6.84; N, 27.18. Found: C, 58.40; H, 7.07; N, 26.99.

(13) H. L. Wheeler and C. O. Johns, *Am. Chem. J.*, **38**, 601 (1907).

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Synthetic Hypoglycemic Agents. I[1]

BY HARRY L. YALE

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A number of heterocyclic sulfhydryl containing compounds have been synthesized for possible application as hypoglycemic agents.

There appears to be a relationship between the free sulfhydryl available in the tissues and diabetes. The work of Houssay and others has indicated that various sulfhydryl containing compounds increase the available –SH in certain tissues and thereby provoke a strong resistance to the diabetogenic effects of alloxan or subtotal pancreatectomy.[2] In an attempt to correlate chemical structure with hypoglycemic activity,[3] a number of sulfur containing organic compounds were synthesized. Houssay, Lott and Martinez[4] have reported on the activities of several of these compounds in alloxan and pancreatic diabetes. This paper will be concerned only with the synthesis of these compounds.

1,4-Dimercaptophthalazine was prepared by the reaction of 1,4-dichlorophthalazine and sodium hydrosulfide[5]; 2,4-dichloroquinazoline and sodium hydrosulfide gave 2,4-dimercaptoquinazoline. 1,10-Decamethylenebis-2-thiourea was synthesized by the sequence of reactions[6]

$$NC(CH_2)_8CN \xrightarrow{LiAlH_4} H_2N(CH_2)_{10}NH_2$$

$$\downarrow \begin{matrix} 1,\ CS_2 + NaOH \\ 2,\ EtO_2CCl \end{matrix}$$

$$SCN(CH_2)_{10}NCS \xrightarrow{NH_3} H_2NCSNH(CH_2)_{10}NHCSNH_2$$

n-Decylaminoacetaldehyde (from the acetal) and thiocyanic acid gave 1-decyl-2-imidazolethiol;

(1) Presented before the Division of Medicinal Chemistry at the 121st Meeting of the American Chemical Society, Milwaukee, Wis., March 31–April 3, 1952.

(2) For reviews on this subject, see B. A. Houssay, *Am. J. Med. Sci.*, **219**, 353 (1950), and C. Martinez, *Acta Physiol. Latinoamericana*, **2**, 135 (1951).

(3) The earlier literature on the hypoglycemic activity of organic sulfur compounds has been reviewed by C. E. Braun, M. B. Mason and C. L. Brown, *J. Chem. Education*, **15**, 261 (1938). See, also, A. Loubatiers, *Compt. rend. soc. biol.*, **138**, 766, 830 (1944); *Arch. internat. physiol.*, **54**, 58 (1946); K. K. Chen, R. C. Anderson and N. Maze, *Proc. Soc. Exptl. Biol.*, **63**, 483 (1946); and D. Bovet and P. Dubost, *Compt. rend. soc. biol.*, **138**, 764 (1944).

(4) B. A. Houssay, W. A. Lott and C. Martinez, *Rev. soc. argentina biol.*, **26**, 335 (1950); *Compt. rend. soc. biol.*, **145**, 591 (1951).

(5) D. Radulescu and V. Georgescu, *Bull. soc. chim.*, **37**, 881 (1925), (*C. A.*, **20**, 184 (1926)) prepared this compound by the reaction of 1,4-dihydroxyphthalazine and P_2S_5. In our hands this method gave a very impure product which was difficult to purify.

(6) The procedure followed was modeled after that described in *Org. Syntheses*, **21**, 81 (1941).