3-*n*-Heptyl-5-cyanouracil.—Thirty-one grams of 3-*n*-heptyl-5-cyanocytosine was treated with 150 ml. of 3 *N* HCl as described in the above paragraph to yield 18 g. (60%) of 3-*n*-heptyl-5-cyanouracil, m.p. 156°.

Anal. Calcd. for $C_{12}H_{17}N_3O_2$: C, 61.32; H, 7.30. Found: C, 61.04; H, 7.32.

Acid Hydrolysis of 5-Carbethoxycytosines.—Twenty-five grams of 3-isoamyl-5-carbethoxycytosine was added to 300 ml. of 3 *N* HCl and refluxed for 3 hours. After this time the expected uracil had not separated and when the solution was made slightly basic with NaOH solution, 18 g. of the original cytosine was recovered. This procedure was repeated with 3-ethyl-5-carbethoxycytosine and starting material was again recovered.

Six grams of 3-isoamyl-5-carbethoxycytosine was added to 100 ml. of 12 *N* HCl and heated on the steam-bath for two hours. Upon cooling 3-isoamyl-5-carboxycytosine hydrochloride crystallized. This was recrystallized from water; yield 5.5 g. or 92%, m.p. 232.5°.

Anal. Calcd. for $C_{10}H_{16}ClN_3O_3$: C, 46.00; H, 5.74; N, 16.18. Found: C, 46.02; H, 6.20; N, 16.15.

Seven grams of 3-ethyl-5-carbethoxycytosine was added to 100 ml. of 12 *N* HCl and treated in the same manner described in the above paragraph to yield 6 g. or 85% of **3-ethyl-5-carboxycytosine hydrochloride**, m.p. 228.5–231.5° dec.

Anal. Calcd. for $C_7H_{10}ClN_3O_3$: Cl, 15.98. Found: Cl, 16.07.

5-Carboxycytosines.—Two-tenths mole of the appropriate β-ureido-α-carboxyacrylonitrile and 21.6 g. (0.4 mole) of sodium methoxide were added to 500 ml. of methanol and the solution refluxed for 12–24 hours. The alcohol was evaporated under reduced pressure (15 mm.). The solid residue was dissolved in a minimum amount of cold water. The solution was acidified with acetic acid and the 5-carboxycytosine was collected. The product was purified by recrystallization from hot water or by dissolving in $NaHCO_3$ solution and reprecipitating with acetic acid. The following carboxycytosines were prepared.

3-Methyl-5-carboxycytosine, yield 57.5%, m.p. 251° dec. *Anal.* Calcd. for $C_6H_7N_3O_3$: C, 42.60; H, 4.17. Found: C, 42.65; H. 4.22.

3-Ethyl-5-carboxycytosine, yield 81%, m.p. 240° dec. *Anal.* Calcd. for $C_7H_9N_3O_3$: C, 45.81; H, 4.95. Found: C, 45.70; H, 5.07.

3-*n*-Butyl-5-carboxycytosine monohydrate, yield 68%, m.p. 208° dec. *Anal.* Calcd. for $C_9H_{15}N_3O_4$: C, 47.20; H, 6.59. Found: C, 47.83; H, 6.48.

3-*n*-Butyl-5-carboxycytosine, yield practically quantitative by drying the monohydrate at 140° for 2 hours, m.p. 210° dec. *Anal.* Calcd. for $C_9H_{13}N_3O_3$: C, 51.25; H, 6.21. Found: C, 51.30; H, 6.11.

3-*n*-Heptyl-5-carboxycytosine, yield 81%, m.p. 224° dec. *Anal.* Calcd. for $C_{12}H_{19}N_3O_3$: C, 56.95; H, 7.56. Found: C, 56.88; H, 7.79.

Decarboxylation of 5-Carboxycytosines. 3-Methylcytosine.—Five grams of 3-methyl-5-carboxycytosine was placed in a Pyrex test-tube and lowered into a Wood metal-bath heated at 250–255°. The carboxycytosine melted with evolution of CO_2. The mass was stirred with a glass rod for 10–15 minutes until the bubbling ceased. The contents of the test-tube were dissolved in hot water. The water solution was clarified with carbon, filtered and evaporated to a small volume. After cooling 3-methylcytosine crystallized. It was collected and recrystallized from hot water; yield 0.7 g. (19%), m.p. 260–265° dec.

Anal. Calcd. for $C_5H_7N_3O$: C, 47.95; H, 5.63. Found: C, 47.89; H, 5.65.

3-*n*-Heptylcytosine.—Ten grams of 3-*n*-heptyl-5-carboxycytosine was heated, in a small flask placed in a Wood metal bath, at 150–170°. After 15 minutes the product was dissolved in ethanol. The solution was treated with carbon, filtered and concentrated on the steam-bath. 3-*n*-Heptylcytosine crystallized and after it was dried, it melted at 169°, yield 3.5 g. (29.5%).

Anal. Calcd. for $C_{11}H_{19}N_3O$: C, 63.10; H, 9.16. Found: C, 62.80; H, 9.07.

1-Methyl-3-*n*-heptyl-5-cyanouracil.—Seventeen grams (0.074 mole) of 3-*n*-heptyl-5-cyanouracil was added to 400 ml. of water containing 3 g. (0.075 mole) of NaOH. The solution was stirred and heated at 45°. While stirring 9.3 g. (0.074 mole) of dimethyl sulfate was added dropwise. After 30 minutes the precipitated solid was collected and recrystallized from a mixture of ethanol and water; yield 16.5 g. (91.5%), m.p. 101°.

Anal. Calcd. for $C_{13}H_{19}N_3O_2$: C, 62.60; H, 7.68. Found: C, 62.81; H, 8.03.

1-Methyl-3-cyclohexyl-5-cyanouracil.—Fifty grams (0.24 mole) of 3-cyclohexyl-5-cyanouracil was treated with 9.6 g. (0.24 mole) of NaOH and 30.2 g. (0.24 mole) of dimethyl sulfate by the procedure described in the above paragraph to yield 30 g. (54.5%) of 1-methyl 3-cyclohexyl-5-cyanouracil, m.p. 175°.

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.75; H, 6.44. Found: C, 61.19; H, 6.82.

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Reactions of Orthoesters with Ureas. II

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RECEIVED APRIL 22, 1955

The reaction sequences that followed the action of orthoesters upon ureas were dependent upon the nature and position of substituents on the urea, the particular orthoester and the reaction conditions. Products obtained were ethoxymethylene, diethoxymethyl, and α-ethoxyethylidineureas, mono- and dicarbamylformamidines, urethans, 2-benzylidinecarbazic esters, 1,3-diarylformamidines, N-formylureas, aryltriazolones and 2-amino-1,3,4-thiadiazoles.

In a preceding paper[1] the reactions of triethyl orthoformate with alkylureas were discussed. The products of these reactions were 1,3-bis-alkylcarbamylformamidines. By varying the reactants and the reaction conditions, products other than 1,3-dicarbamylformamidines may be obtained, often in excellent yields. This paper is concerned with reactions of orthoesters and ureas to yield (1) alkoxymethylene and dialkoxymethylureas, (2) arylcarbamylformamidines, (3) urethans, (4) triazolones and (5) thiadiazoles.

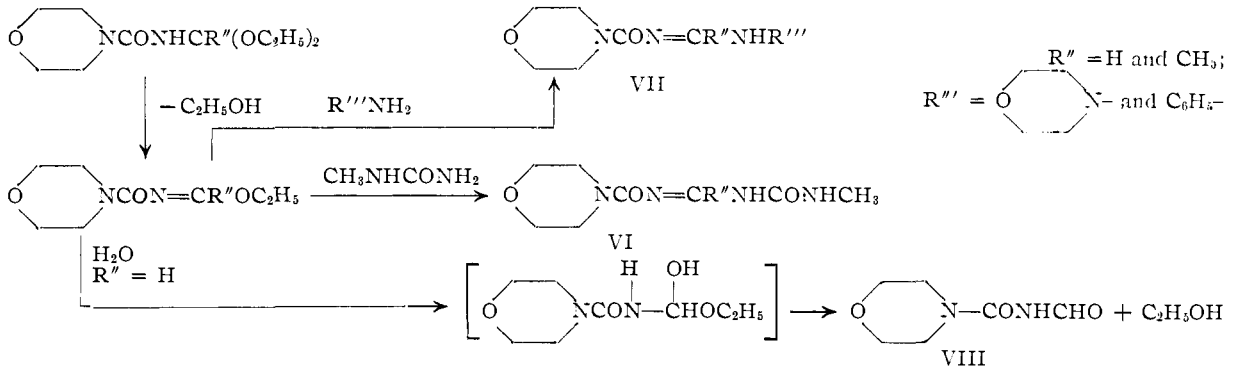
(1) C. W. Whitehead, THIS JOURNAL, **75**, 671 (1953).

Although dialkoxymethylureas IV and alkoxymethyleneureas V have been proposed as intermediate products, they were not generally isolated when alkylureas were heated with orthoesters. The final products from such reactions were 1,3-dicarbamylformamidines. When, however, acetic anhydride, alkylureas and orthoesters were heated together, the compounds IV and V were obtained as major products of the reaction. Thus, 1-diethoxymethylene-3-ethylurea (IV, R = C_2H_5, R′ = R″ = H) was obtained when ethylurea was allowed to react with triethyl orthoformate II and

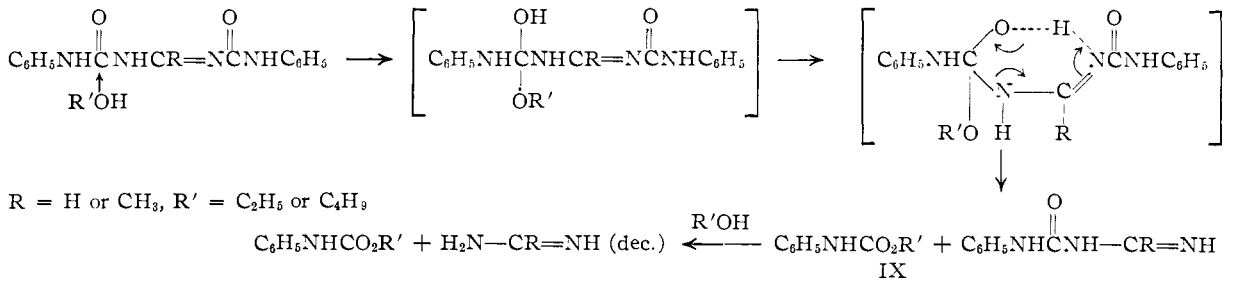
acetic anhydride. Morpholine-4-carboxamide with II and acetic anhydride gave both the diethoxymethylene- and the ethoxymethyleneurea (IV and V). All the reactions so far examined of triethyl orthoacetate (III) and acetic anhydride with alkyl- or arylureas I have given ethoxyethylidine derivatives (V, R″ = CH_3).

$$RR'NCONH_2 + R''C(OC_2H_5)_3 + 2(CH_3CO)_2O \longrightarrow$$
I II and III
$$RR'NCONHCR''(OC_2H_5)_2 \longrightarrow$$
IV
$$RR'NCON{=}CR''OC_2H_5 + 2CH_3CO_2C_2H_5 + 2CH_3CO_2H$$
V

Reactions of the diethoxy and ethoxy compounds IV and V with amines, ureas and water yielded solid derivatives. Morpholine-4-(ethoxymethylenecarboxamide) and morpholine-4-(α-ethoxyethylidinecarboxamide) reacted spontaneously with amines to yield the corresponding aminomethyleneureas (VII, R″ = H) and α-aminoethylidineureas (VII, R″ = CH_3). When morpholine-4-(ethoxymethylenecarboxamide) was heated with methylurea the expected 1,3-dicarbamylformamidine (VI) was produced. Hydrolysis of morpholine-4-(ethoxymethylenecarboxamide) resulted when it was allowed to stand in the air at room temperature. The product of this mild hydrolysis was the N-formylurea (VIII). On the other hand, morpholine-4-(diethoxymethylenecarboxamide) did not undergo hydrolysis by standing in air. Ethanol slowly was lost, however, when the diethoxymethyleneurea was warmed, and the resulting morpholine-4-(ethoxymethylenecarboxamide) again yielded VIII after standing in air.



When N-arylureas reacted with either triethyl orthoformate or triethyl orthoacetate in the *absence* of acetic anhydride, N-arylurethans IX were produced. The conversion of an arylurea by the orthoester to a urethan was entirely unexpected. The best explanation was that the urethans were formed as a result of the presence of alcohol in the reaction mixture. When acetic anhydride was added to tie up the alcohol produced during the reaction, the urethans were not formed. Arylureas reacted rapidly with triethyl orthoformate in the presence of acetic anhydride under mild conditions to give almost quantitative yields of 1,3-bis-arylcarbamylformamidines. It seemed probable that the arylureas reacted with orthoesters in the absence of acetic anhydride to also yield 1,3-bis-arylcarbamylformamidines which in turn readily underwent alcoholysis to yield the urethans. The possibility that 1,3-bis-arylcarbamylformamidines underwent alcoholysis to yield urethans was tested. When 1,3-bis-phenylcarbamylformamidine was refluxed with ethanol, phenylurethan was obtained and when refluxed with *n*-butyl alcohol the corresponding *n*-butyl phenylcarbamate resulted. The following mechanism is proposed for the alcoholysis.

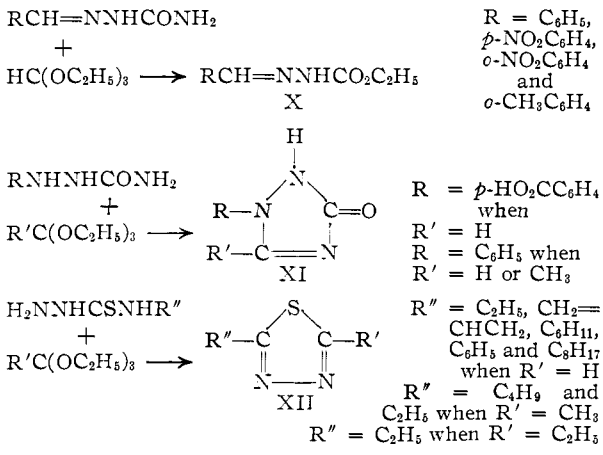


In the reactions of arylureas with triethyl orthoformate it is not probable that the arylureas underwent alcoholysis. Although arylureas were found to undergo alcoholysis when refluxed with high boiling alcohols, these ureas did not react with boiling ethanol. When 1,3-diphenylurea was refluxed with cyclohexanol and also with isoamyl alcohol the respective products were cyclohexyl carbanilate and isoamyl carbanilate. In a like manner 1-ethyl-3-phenylurea and 1-acetyl-3-phenylurea both yielded *n*-butyl carbanilate when refluxed with *n*-butyl alcohol. When 1,1,3-triphenylurea was heated with *n*-butyl alcohol an excellent yield of *n*-butyl N,N-diphenylcarbanate was obtained. In this last example formation of an intermediate isocyanate is impossible and it is suspected that isocyanates were not intermediates in the other cases.

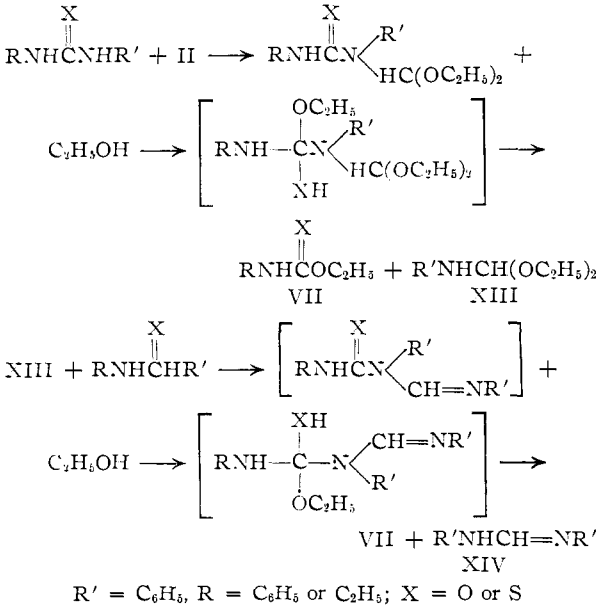
The reaction of triethyl orthoformate with N-arylureas was found to be a convenient and general

method for the preparation of N-arylurethans. In a like manner N-allylurea, N-α-pyridylurea and the semicarbazones from benzaldehyde, *p*-nitrobenzaldehyde, *o*-nitrobenzaldehyde and *o*-methoxybenzaldehyde yielded the corresponding urethans and ethyl 2-benzylidinecarbazates (X).

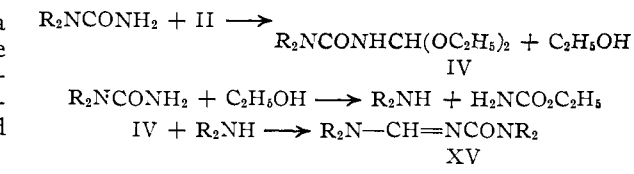
Cleavage of the carbamyl bond did not occur when the orthoester could effect a ring closure. 1-Arylsemicarbazides reacted with triethyl orthoformate and triethyl orthoacetate to yield aryltriazolones XI. 4-Alkyl- and 4-arylthiosemicarbazides reacted with the orthoester to produce 2-amino-1,3,4-thiadiazoles (XII).



Cleavage of the carbamyl bond occurred readily as a result of the action of II on 1,1- and 1,3-disubstituted ureas. Consequently 1,3-diaryl-2-thio-, 1-alkyl-3-aryl- and 1,3-diarylureas yielded 1,3-diphenylformamidine (XIV) and N-substituted carbamates VII. Formation of these products could again be explained by alcoholysis of the carbamyl group and is proposed as



A similar mechanism is proposed for the formation of monocarbamylformamidines XV and urethan from 1,1-dialkyl- and 1,1-diarylureas.



Formation of the secondary amine did occur when morpholine-4-carboxamide and *n*-butyl alcohol yielded morpholine and butylcarbamate. This mechanism also requires that the secondary amine exist unchanged, or slowly reacted upon, by an excess of II. Morpholine and diphenylamine were each refluxed for 36 hours with II and both amines were recovered.

Acknowledgments.—The authors gratefully thank W. L. Brown, H. L. Hunter, G. M. Maciak and G. Beckmann for the microanalyses and Drs. Reuben Jones and Earle Van Heyningen for valuable suggestions.

Materials.—N-Aryl-, N-alkyl-, N,N-diaryl- and N,N-dialkylureas were prepared by heating an aqueous solution of the appropriate amine hydrochloride and sodium cyanate. Carbanilide and triethyl orthoacetate were obtained from Distillation Products, Inc., Rochester, N. Y., and triethyl orthoformate from Kay–Fries Co., New York, N. Y. 1,1,3-Triphenylurea was prepared from diphenylamine and phenyl isocyanate. Alkyl- and arylisothiocyanates were prepared by the action of lead nitrate on the dithiocarbamates. The 4-substituted thiosemicarbazides were then obtained from the isothiocyanate and hydrazine.

Experimental

1-Ethyl-3-diethoxymethyleneurea.—A mixture of 200 g. (2.27 moles) of ethylurea, 333 g. (3.27 moles) of acetic anhydride and 500 g. (3.38 moles) of triethyl orthoformate was heated at 60–70° for 12 hours. The resulting mixture was fractionated through a glass spiral column. The fraction collected at 174.5° (lit. 172°)[2] and 760 mm., $n^{25}D$ 1.4200, was N-ethylurethan; yield 30 g. or 11%.

A second fraction, 66.5 g. or 15%, b.p. 102° at 14 mm., $n^{25}D$ 1.4370, analyzed for 1-ethyl-3-diethoxymethyleneurea.

Anal. Calcd. for $C_8H_{18}N_2O_3$: C, 50.40; H, 9.55; N, 14.76. Found: C, 50.14; H, 9.29; N, 14.49.

Morpholine-4-(diethoxymethylcarboxamide) and Morpholine-4-(ethoxymethylenecarboxamide).—A mixture of 130 g. (1.0 mole) of morpholine-4-carboxamide, 306 g. (3.0 moles) of acetic anhydride and 148 g. (1.0 mole) of triethyl orthoformate was refluxed for 8 hours. Ethyl acetate and acetic acid were both removed at 10 mm. on the steam-bath. The remaining oil was distilled through a short glass spiral column to yield 129 g. of oil, b.p. 90–100° at 1.5 mm. This was then fractionated through a Vigreux column (12 mm. o.d., 30 in. long) fitted with a partial take-off head. The first fraction, 5 g., b.p. 50–60° at 0.3 mm. partially crystallized and was recrystallized from ethyl acetate to yield 3 g., 2.3%, of solid, m.p. 76°, that was not identified.

Anal. Calcd. for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.71. Found: C, 46.17; H, 7.20; N, 10.39.

The second fraction distilled at 65° and 0.3 mm. and was morpholine-4-(diethoxymethylenecarboxamide), yield 60 g. or 26%.

Anal. Calcd. for $C_{10}H_{20}N_2O_4$: N, 12.09. Found: N, 12.29.

The third fraction distilled at 100° and 0.9 mm., and was morpholine-4-(ethoxymethylenecarboxamide); yield 34 g. or 18%.

Anal. Calcd. for $C_8H_{14}N_2O_4$: N, 15.05. Found: N, 15.19.

(2) L. Schreiner, *J. prakt. Chem.*, [2] **21**, 125 (1880).

TABLE I

RNHCNHCH=NCNHR (O above each C)

R	Formula	M.p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
C_6H_5	$C_{16}H_{14}N_4O_2$	220	90	63.84	64.03	4.99	5.18	19.85	19.95
2,6-$(CH_3)_2C_6H_3$	$C_{19}H_{22}N_4O_2$	267 d.	85					16.55	16.53
p-$C_2H_5C_6H_4$	$C_{19}H_{22}N_4O_4$	222	86					15.13	15.46

1-Ethyl-3-α-ethoxyethylidineurea.—A mixture of 44 g. (0.5 mole) of ethylurea, and 100 g. (0.61 mole) of triethyl orthoacetate was heated at 60° for 5 hours. The solution was concentrated on the steam-bath at 15 mm. pressure and cooled. Fifteen grams of ethylurea crystallized from solution and was separated by filtration. The remaining oil was distilled through a small Vigreux column to yield 34 g. (65%) of 1-ethyl-3-α-ethoxyethylidineurea, b.p. 88° at 1.4 mm., $n^{25}D$ 1.4580.

Anal. Calcd. for $C_7H_{14}N_2O_2$: N, 17.73. Found: N, 17.43.

1-Cyclohexyl-3-α-ethoxyethylidineurea.—A solution of 35 g. (0.248 mole) of cyclohexylurea in 100 ml. of triethyl orthoacetate was refluxed for 10 hours. The solution was concentrated on the steam-bath at 10 mm. The remaining sirup was allowed to cool and crystallize. The white needles were collected on a büchner funnel and recrystallized from ether; m.p. 85°, yield 36.5 g. or 72%.

Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.30; H, 9.45; N, 13.19. Found: C, 62.30; H, 9.45; N, 12.91.

Morpholine-4-(α-ethoxyethylidinecarboxamide).—A mixture of 65 g. (0.5 mole) of morpholine-4-carboxamide, 153 g. (1.5 moles) of acetic anhydride and 81 g. (0.5 mole) of triethyl orthoacetate was boiled for 10 minutes. The heating was discontinued and the mixture allowed to stand for one-half hour. The mixture was then fractionated through a Vigreux column, 30 inches long and 12 mm. in diameter, to yield 70 g. (70%) of morpholine-4-(α-ethoxyethylidinecarboxamide), b.p. 93° at 0.7 mm., $n^{25}D$ 1.4830.

Anal. Calcd. for $C_9H_{16}N_2O_3$: N, 13.99. Found: N, 14.07.

1-Aryl-3-α-ethoxyethylidineureas.—One-tenth mole of an N-arylurea was added to 30.6 g. (0.3 mole) of acetic anhydride and 50 ml. of triethyl orthoacetate and heated to boiling on the hot-plate. The flask was removed and allowed to stand for one-half hour. During part of this time the mixture continued to boil. The solution was concentrated at 15 mm. on the steam-bath and the residual oil allowed to cool and crystallize. This was recrystallized from a mixture of ether and petroleum ether. The following were prepared:

1-*p*-**Phenethyl-3α-ethoxyethylidineurea**, m.p. 103–103.5°, yield 94%. *Anal.* Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.20; H, 7.14; N, 11.14.

1-**Phenyl-3α-ethoxyethylidineurea**, m.p. 78°, yield 85%. *Anal.* Calcd. for $C_{11}H_{14}N_2O_2$: N, 13.72. Found: N, 13.72.

Hydrolysis of Morpholine-4-(ethoxymethylenecarboxamide). N-Formylmorpholine-4-carboxamide (VIII).—Five grams (0.027 mole) of morpholine-4-(ethoxymethylenecarboxamide) was allowed to stand 5 days in an open beaker until the oil became completely solid. This solid was recrystallized from a mixture of ether and ethyl acetate to yield 4.1 g. or 97% of N-formylmorpholine-4-carboxamide, m.p. 155°.

Anal. Calcd. for $C_6H_{10}N_2O_3$: C, 45.55; H, 6.37; N, 17.72. Found: C, 45.76; H, 6.28; N, 17.66.

N-(α-Anilinoethylidine)-morpholine-4-carboxamide.—Morpholine-4-(α-ethoxyethylidinecarboxamide) was mixed with 0.93 g. (0.01 mole) of aniline and allowed to stand for 2 days. The resulting solid was recrystallized from a mixture of ethyl acetate and ether; yield 1.05 g. (42%), m.p. 152–154°.

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 17.02. Found: C, 63.13; H, 6.98; N, 17.47.

N-(α-Morpholinoethylidine)-morpholine-4-carboxamide.—Two grams (0.01 mole) of morpholine-4-(α-ethoxyethylidinecarboxamide) and 0.87 g. (0.01 mole) of morpholine were treated in the above manner; yield 1.5 g. (62%), m.p. 98–99°.

Anal. Calcd. for $C_{11}H_{19}N_3O_3$: C, 54.75; H, 7.94; N, 17.42. Found: C, 54.79; H, 8.16; N, 17.21.

1-Morpholinocarbonyl-3-methylcarbamylformamidine.—One and eight-tenths grams (0.01 mole) of morpholine-4-(ethoxymethylenecarboxamide) was added to 0.74 g. (0.01 mole) of methylurea and the mixture heated at 100° for 2 hours. The residue was allowed to stand and crystallize. The crystals were collected and recrystallized from ethyl acetate; yield 0.5 g. (42%), m.p. 202°.

Anal. Calcd. for $C_8H_{14}N_4O_3$: C, 44.85; H, 6.58; N, 26.15. Found: C, 44.72; H, 6.45; N, 26.31.

N-Aryl- and N-Alkylurethans from N-Aryl-, N-Alkylureas and Triethyl Orthoesters. Method A.—One-third mole of the N-arylurea or the N-alkylurea was added to 250 ml. of triethyl orthoformate or 200 ml. of triethyl orthoacetate and refluxed for 8 hours. The solution was concentrated on the steam-bath at 15 mm. The resulting sirup was crystallized from ether or distilled through a Vigreux column. The following urethans were obtained:

5-Chloro-2-methylphenylurethan, m.p. 95°, yield 98%. *Anal.* Calcd. for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.22; H, 5.45; N, 6.79.

p-**Diethylaminophenylurethan**, b.p. 168° at 1.5 mm., yield 85.8%, hydrochloride, m.p. 145°. *Anal.* Calcd. for $C_{13}H_{21}ClN_2O_2$: N, 10.27. Found: N, 10.51.

p-**Chlorophenylurethan**, yield 74%, m.p. 69° (lit. 68°).[3]

p-**Methoxyphenylurethan**, yield 58%, m.p. 65° (lit. 65°).[4]

α-**Naphthylurethan**, yield 52%, m.p. 79° (lit. 79°).[5]

Allylurethan, yield 38%, b.p. 87° at 8 mm. (192° at 760 mm.) (lit. 194.5–195° at 768 mm.).[6]

α-**Pyridylurethan**, yield 72%, b.p. 115° at 3.0 mm., m.p. 105° (lit. 105°),[7] along with *sym*-α-pyridylurea, b.p. 170° at 3.0 mm., m.p. 171°, yield 7%.

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.70; H, 4.72; N, 26.15. Found: C, 61.54; H, 4.62; N, 25.92.

Method B. N-Phenylurethan.—A mixture of 68 g. (0.5 mole) of phenylurea, 51 g. (0.5 mole) of acetic anhydride and 177 g. (1.2 moles) of triethyl orthoformate was refluxed for 4 hours. The mixture was distilled through a Vigreux column and the fraction boiling at 115° at 0.75 mm. was collected. This fraction crystallized and was recrystallized from a mixture of petroleum ether and ether, m.p. 59–60°, yield 70 g. or 83%.

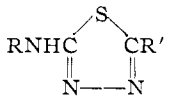
Phenylurea was treated in this same manner with ethyl orthoacetate in the absence of acetic anhydride to yield N-phenylurethan in 61% yield.

1,3-Bis-arylcarbamylformamidines.—One-tenth mole of the N-arylurea was added to 33.9 g. (0.33 mole) of acetic anhydride and 100 ml. of triethyl orthoformate and warmed to the boiling point. The formamidine separated and was collected on a büchner funnel. Phenylurea yielded the formamidine by standing at room temperature for 0.5 hour with the orthoformate and acetic anhydride. The formamidines (Table I) were insoluble or only slightly soluble in ethyl acetate, ethanol, benzene, water and ethylene dichloride and were recrystallized from a mixture of dimethylformamide and ethyl acetate.

Alcoholysis of 1,3-Bis-phenylcarbamylformamidine.—Ten grams of 1,3-bis-phenylformamidine was added to 100 ml. of ethanol and the alcohol refluxed for 12 hours. The resulting solution was concentrated on the steam-bath under reduced pressure (15 mm.) and then cooled. The residue was extracted with ether and 1.5 g. of undissolved starting formamidine was recovered. The ether solution was concentrated and cooled to yield 1.2 g. (17.7%) of N,N'-di-

(3) H. Vittenet, *Bull. soc. chim. France*, [3] **21**, 954 (1899).
(4) O. Brunner and R. Worhl, *Monatsh.*, **63**, 374 (1933).
(5) A. W. Hofmann, *Ber.*, **3**, 657 (1870).
(6) S. Nirdlinger and S. F. Acree, *Am. Chem. J.*, **43**, 381 (1910).
(7) R. Camps, *Arch. Pharm.*, **240**, 350 (1902).

TABLE II



R	R′	Formula	M.p., °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
C_2H_5	H	$C_4H_7N_3S$	70	60	37.21	37.41	5.46	5.54	32.55	32.71
CH_2=$CHCH_2$	H	$C_5H_7N_3S$	73[13]	56						
C_2H_5	CH_3	$C_5H_9N_3S$	108	70	41.97	42.16	6.34	6.41	29.36	29.12
C_2H_5	C_2H_5	$C_6H_{11}N_3S$	49–50	57	45.85	46.09	7.05	6.92	26.74	26.75
C_4H_9	CH_3	$C_7H_{13}N_3S$	103	71	49.16	49.14	7.66	7.89	24.55	24.46
C_6H_5	H	$C_8H_7N_3S$	173[14]	81						
C_6H_{11}	H	$C_8H_{13}N_3S$	165	72	52.44	52.42	7.15	7.27	22.94	23.10
C_8H_{17}	H	$C_{10}H_{19}N_3S$	92–93	76	56.32	56.36	8.97	8.98	19.72	19.50

phenylurea. The remaining ether solution was further concentrated to yield 9.1 g. of oil. This was distilled through a small Vigreux column to give 4.5 g., 45%, of N-phenylurethan, b.p. 111° at 1.5 mm., m.p. 59°. Phenylurea, 0.8 g. or 21%, was collected in the condenser.

1,3-Bis-phenylcarbamylformamidine, 5 g., was treated in a like manner with 50 ml. of *n*-butyl alcohol to yield 4.6 g. (66%) of N-butylcarbanilate 60–61°.[8]

Alcoholysis of Ureas.—Fifty grams of the urea was added to 150 ml. of *n*-butyl alcohol, cyclohexanol or isoamyl alcohol and refluxed for 1–3 days. The solution was concentrated on the steam-bath at 10–15 mm. The carbamate was crystallized from petroleum ether or a mixture of ether and petroleum ether.

1-Ethyl-3-phenylurea and *n*-butyl alcohol yielded *n*-butylcarbanilate, m.p. 60–61°,[9] yield 88%.

1-Acetyl-3-phenylurea and *n*-butyl alcohol also gave *n*-butyl carbanilate, 58%.

1,3-Diphenylurea and cyclohexanol yielded cyclohexyl carbanilate, m.p. 81–82° (lit. 82°),[10] 87%.

1,3-Diphenylurea and isoamyl alcohol yielded isoamyl carbanilate, b.p. 135° at 0.8 mm., 44%.

Anal. Calcd. for $C_{12}H_{17}NO_2$: N, 6.76. Found: N, 7.06.

1,1,3-Triphenylurea and *n*-butyl alcohol yielded *n*-butyl N,N-diphenylcarbamate, b.p. 158° at 8 mm., m.p. 61.5–62°, yield 95%.

Anal. Calcd. for $C_{17}H_{19}NO_2$: N, 7.30. Found: N, 7.32.

Morpholine-4-carboxamide and *n*-butyl alcohol yielded morpholine and *n*-butyl carbamate, m.p. 53–54° (lit. 53–54°),[9] yield 15%.

Ethyl 2-Benzylidinecarbazates (X).—One hundred and fifty milliliters of triethyl orthoformate was added to 0.5 mole of the semicarbazone prepared from one of the following aldehydes: benzaldehyde, *p*-nitrobenzaldehyde, *o*-nitrobenzaldehyde and *o*-methoxybenzaldehyde. The mixture was refluxed for three days. The resulting solutions were concentrated on the steam-bath at 10–15 mm. The solid product was recrystallized from ethyl acetate. The following ethyl 2-benzylidinecarbazates were prepared:

Ethyl 2-*p*-nitrobenzylidinecarbazate, m.p. 147–148°, yield 25%. *Anal.* Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.75; H, 4.68. Found: C, 50.49; H, 4.86.

Ethyl 2-*o*-methoxybenzylidinecarbazate, m.p. 120°, yield 20%. *Anal.* Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.20; H, 6.28; N, 12.62. Found: C, 59.05; H, 6.28; N, 12.76.

Ethyl 2-*o*-nitrobenzylidinecarbazate, m.p. 130° (lit. 130–131°),[11] yield 40%.

Ethyl 2-benzylidinecarbazate, m.p. 137° (lit. 135–136°),[12] yield 29%.

2-Amino-1,3,4-thiadiazoles (XII).—One-fourth mole of the 4-alkylthiosemicarbazide or 4-aryl-thiosemicarbazide was added to 75 ml. of triethyl orthoformate and heated on the steam-bath at 60–80° for 36 hours. The 3-amino-1,3,4-thiadiazole crystallized upon cooling and was recrystallized from ethyl acetate (Table II).

4-Alkyl-thiosemicarbazides were treated in a like manner with triethyl orthoacetate and triethyl orthopropionate to yield 2-amino-5-methyl- and 2-amino-5-ethyl-1,3,4-thiadiazoles (Table II).

1-Phenyl-5-methyl-1,2,4-triazolone.—Twenty-five grams (0.165 mole) of 1-phenylsemicarbazide was added to 50 ml. of triethyl orthoacetate and refluxed for 24 hours. The solution was concentrated on the steam-bath at 15 mm. The solid 1-phenyl-5-methyl-1,2,4-triazolone was recrystallized from alcohol, yield 16 g. or 60%, m.p. 183°.

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.56; H, 5.11; N, 23.87.

1-Phenyl-1,2,4-triazolone.—Fifty grams (0.33 mole) of 1-phenylsemicarbazide was treated with 150 ml. of triethyl orthoformate in the above manner to yield 40 g. (75%) of 1-phenyl-1,2,4-triazolone, m.p. 273–274° (lit. 273–274°).[15]

1-*p*-Carboxyphenyl-1,2,4-triazolone.—Forty-five grams (0.25 mole) of 1-*p*-carboxyphenylsemicarbazide was added to 250 ml. of triethyl orthoformate and refluxed for 36 hours. The mixture was concentrated at 10 mm. on the steam-bath, then cooled. The solid was collected and washed with hot ethanol; yield 51 g. or 98%. A sample was dissolved in hot aqueous sodium bicarbonate, filtered and acidified with acetic acid. The solid was collected and washed thoroughly with hot water; unmelted at 300°.

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.68; H, 3.44; N, 20.48. Found: C, 52.44; H, 3.59; N, 20.42.

Reactions of Triethyl Orthoformate with 1,3-Disubstituted Ureas. 1,3-Diphenylurea.—Fifty-three grams (0.25 mole) of 1,3-diphenylurea was heated at refluxing temperature with 300 ml. (an excess) for 12 hours. The solution was concentrated at 10 mm. on the steam-bath. The residual oil was dissolved in a 50% mixture of ether and petroleum ether and cooled in the refrigerator to yield 9 g. or 18% of 1,3-diphenylformamidine, m.p. 136–137° (lit. 135–136°).[16] The filtrate was concentrated, petroleum ether added to incipient turbidity and cooled to yield phenylurethan, 14.5 g. or 35%.

1,3-Dibenzylurea.—Fifty grams (0.204 mole) of 1,3-dibenzylurea was treated with 200 ml. of triethyl orthoformate in the above manner. The residual oil was distilled through a Widmer column to yield 24.7 g., 72%, of benzylurethan, b.p. 97° at 0.35 mm., $n^{25}D$ 1.5149, m.p. 48–49° (lit. 48–49°).[17]

1-Ethyl-3-phenylurea.—Forty grams (0.24 mole) of 1-ethyl-3-phenylurea was heated with 200 ml. of triethyl orthoformate as above, and the mixture distilled to yield 48 g. of oil, b.p. 50–150° at 1.5 mm. This was fractionated through a glass spiral column to yield 26.5 g. or 61% of phenylurethan, m.p. 59°, and 7.5 g. or 31% of 1,3-diphenylformamidine, m.p. 136°.[16]

1,3-Diphenylthiourea.—Fifty-nine grams (0.26 mole) of 1,3-diphenylthiourea was added to 200 ml. of triethyl orthoformate and refluxed for 12 hours. The mixture was concentrated on the steam-bath at 10 mm. A mixture of 30% ether and 70% petroleum ether was added and 6 g. (11.7%) of 1,3-diphenylformamidine, m.p. 135°, remained undis-

(8) C. Weismann and S. F. Garrard, *J. Chem. Soc.*, **117**, 328 (1920).

(9) T. L. Davis and S. C. Lane, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 140.

(10) M. L. Bouveault, *Bull. soc. chim. France*, [3] **29**, 1052 (1903).

(11) D. N. Majumbar and P. C. Guha, *J. Indian Chem. Soc.*, **10**, 685 (1933).

(12) J. Thiele and A. Lachman *Ann.*, **288**, 293 (1895).

(13) The reported m.p. is 73°: G. Pulvermacher, *Ber.*, **27**, 627 (1894).

(14) The reported m.p. is 173°: G. Pulvermacher, *ibid.*, **27**, 617 (1894).

(15) O. Widman, *ibid.*, **26**, 2613 (1893).

(16) W. Weith, *ibid.*, **9**, 455 (1876).

(17) A. Hantzsch, *ibid.*, **31**, 180 (1898).

solved. The ether solution was evaporated and the oil was dissolved in petroleum ether and cooled to yield 28 g. or 59% of ethyl phenylthiocarbamate, m.p. 70° (lit. 71–72°).[18]

Reactions of Triethyl Orthoformate with 1,1-Disubstituted Ureas. N-(Morpholine-4-methylene)-morpholine-4-carboxamide.—Two hundred and twenty grams (1.67 moles) of morpholine-4-carboxamide was added to 400 ml. (2.4 moles) of triethyl orthoformate and refluxed for 7 days. The solution was cooled in the refrigerator and 114 g. of solid crystallized. The remaining oil was allowed to stand and another 59 g. of solid was obtained. The combined solids were recrystallized from ethyl acetate to yield 149 g. (77%) of N-(morpholine-4-methylene)-morpholine-4-carboxamide, m.p. 126–127°.

Anal. Calcd. for $C_{10}H_{17}N_3O_3$: C, 52.80; H, 7.55; N, 18.52. Found: C, 52.50; H, 7.28; N, 18.92.

The oil remaining (51 g.) in the filtrate was distilled through a Widmer column to yield 20 g. (27%) of urethan, b.p. 52° at 0.4 mm., m.p. 47.5–48.5°. A mixed melting of the latter and an authentic sample of urethan was not depressed.

One and eight-tenths grams (0.01 mole) of morpholine-4-(ethoxymethylenecarboxamide) was allowed to stand for 3 days with 0.87 g. (0.01 mole) of morpholine. The solid was recrystallized from ethyl acetate to yield 1.5 g. (65%) of N-(morpholine-4-methylene)-morpholine-4-carboxamide, m.p. 126°.

1-(N,N-Diphenylcarbamyl)-3,3-diphenylformamidine.—Thirty grams (0.14 mole) of 1,1-diphenylurea, 30 g. (0.30 mole) of acetic anhydride and 200 ml. of triethyl orthoformate were refluxed for 12 hours. The solution was concentrated at 15 mm. on the steam-bath. Ether was added to the residue and 9 g. or 34% of 1-(N,N-diphenylcarbamyl)-3-diphenylformamidine remained undissolved. This was recrystallized from ethyl acetate, m.p. 174°.

Anal. Calcd. for $C_{26}H_{20}N_3O$: C, 79.95; H, 5.15; N, 10.75. Found: C, 80.49; H, 5.23; N, 10.58.

The ether solution was concentrated and allowed to stand. 1,1-Diphenyl-3-formylurea (3 g. or 8.8%) separated and was recrystallized from ethyl acetate, m.p. 148°.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.78; H, 5.01; N, 11.62. Found: C, 70.02; H, 4.79; N, 11.52.

The remaining oil was distilled through a Widmer column to yield 5 g. (40%) of ethyl urethan, b.p. 68° at 0.5 mm., and 5 g. or 16.4% of diphenylurethan, b.p. 145–160° at 1–2 mm. The latter crystallized from a mixture of ether and petroleum ether, m.p. 72° (lit. 72°).[19]

(18) C. Leibermann, *Ann.*, **207**, 145 (1881).

(19) O. Meister, *Ber.*, **5**, 284 (1872).

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, STATE UNIVERSITY OF IOWA]

The Acid Strength of the –SH Group in Cysteine and Related Compounds

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RECEIVED JUNE 16, 1955

The ultraviolet absorption of the mercaptide ion has been utilized to determine the relative proton affinity of the sulfur and nitrogen functions in a series of aminothiols. For those compounds which show a break in the spectrophotometric titration curve, all four possible pK's were calculated. The heat of dissociation of the –SH group was found to be about 6.5 kcal. by two independent methods. A simple spectrophotometric assay for mixtures of aminothiols is described. The implications of these findings for the mechanism of oxidation of –SH groups to disulfides and for other reactions of biological interest are discussed.

Introduction

The ionic equilibria of compounds which contain both a sulfhydryl and an ammonium group have been the subject of much discussion, since the relative contribution of each of these groups to the dissociation of the two protons could not be determined unequivocally. Reasoning mainly by analogy, three main viewpoints have been put forward: (1) The higher pK was assigned to the –SH group.[1] (2) Peters[2] and more recently Calvin[3] have reversed this assignment. (3) Edsall, as cited by Ryklan and Schmidt,[4] considered both pK values to be mixed ones, since he assumed that the intrinsic proton affinities of the sulfur and nitrogen are about the same.

A decision between these alternatives is difficult in the absence of a method which would permit a distinction between the ionized and un-ionized form of either of the two ionizing groups. The finding by Noda, *et al.*,[5] that butyl mercaptan absorbs ultraviolet light in strongly alkaline, but not in strongly acid, solution suggested a means of measuring the concentration of the RS^- form spectrophotometrically. This property was therefore used in the work presented here to determine the acid strength of the thiol group and its relation to the ammonium group in a series of aminothiols.

(1) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943, p. 84.

(2) L. Peters, Thesis, University of Leeds, 1947.

(3) M. Calvin in "Glutathione," Academic Press, Inc., New York, N. Y., 1954, p. 9.

(4) L. R. Ryklan and C. L. A. Schmidt, *Arch. Biochem.*, **5**, 89 (1944).

(5) L. H. Noda, S. A. Kuby and H. A. Lardy, THIS JOURNAL, **75**, 913 (1953).

Experimental

All spectrophotometric measurements were made with a Beckman Model DU spectrophotometer equipped with "Thermospacers" for measurements at constant temperature (±0.5°). The pH measurements were carried out with a Beckman Model G, and in some cases a Beckman Model GS, pH meter, using a Beckman Type E glass electrode because of its high sensitivity in alkaline solution. All pH measurements were made at the same temperature as the corresponding spectrophotometric readings. The buffer system used for this investigation was a mixture of phosphoric and boric acids which was titrated to the required pH with NaOH and diluted to a final concentration of 0.02 M in each acid. This buffer was sufficient to cover the entire pH range used. All solutions were made up with distilled water which had been passed through Amberlite MB1 mixed anion- and cation-exchange resin.

For spectrophotometric measurements 0.10 ml. of a 1.5 to 2 $\times 10^{-2}$ M solution of the thiol was added from a Syringe Microburet (Micro-Metric Instrument Co., Cleveland, Ohio) to 10 ml. of the buffer solution. The absorption spectrum was determined immediately after mixing, using the corresponding buffer as the blank. All experiments were carried out at 23° unless otherwise stated.

The thiols used were obtained from the following sources: glutathione and L-cysteinyl-glycine, Schwarz Laboratories, Mount Vernon, N. Y.; L-cysteine hydrochloride, Nutritional Biochemicals Corporation, Cleveland, Ohio; DL-homocysteine, General Biochemicals Inc., Chagrin Falls, Ohio;