Studies on the Formation and Transformation of Esters. LXXX.[1] On the Reaction of Isothiocyanates and Phenyl Isocyanate with Hydrazinoethanol and Hydrazinoethyl Hydrogen Sulfate

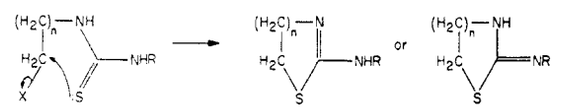
JOSEPH RABINOWITZ,[2] SHERWOOD CHANG, J. M. HAYES, AND FRITZ WOELLER

Exobiology Division, Ames Research Center, NASA, Moffett Field, California 94035

Received July 9, 1968

Reactions of hydrazinoethanol (**3a**) and hydrazinoethyl hydrogen sulfate (**3b**) with phenyl isothiocyanate take place at the substituted nitrogen atom. The corresponding monophenylthiocarbamoyl derivatives undergo ring closure to **6** in hydrochloric acid and 1 *N* sodium hydroxide, respectively. The N,N′-bis(phenylthiocarbamoyl) derivative of **3b** is converted into **7** in alkaline medium, whereas that of **3a** is transformed into **6** and **9** (**a** or **b**) in acid medium. Monothiocarbamoylation of **3b** with *o*-methoxycarbonylphenyl isothiocyanate occurs at the unsubstituted nitrogen atom, yielding **11a** upon cyclization in HCl. Monophenylcarbamoylation of **3a** or **3b** takes place at the substituted nitrogen atom. The reaction of **3a** with a molar excess of phenyl isocyanate affords the N,N′-bis(phenylcarbamoyl) derivative. The reaction of **3b**, however, appears to afford mixtures of mono- and N,N′-bis(phenylcarbamoyl) derivatives; cyclization in 1 *N* NaOH yields **14** and **15**, respectively.

Previous papers in this series have reported that the N-thiocarbamoyl derivatives of 2-aminoethyl and 3-aminopropyl alcohols[3] or their orthophosphate[3,4] and sulfate monoesters[4-6] undergo ring closure to yield heterocyclic bases containing either endo- (**1a**) or exocyclic (**1b**) C=N double bonds.



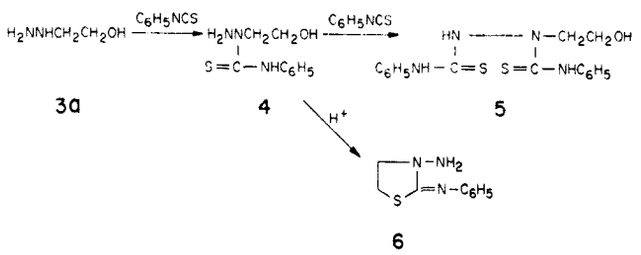
N-Arylcarbamoyl aminoethyl or aminopropyl sulfate monoesters also undergo ring closure to yield five- or six-membered cyclic ureas **2**.[7]

2

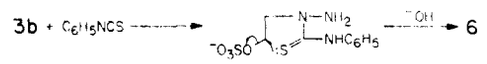
Therefore, it was of further interest to extend these reactions to hydrazinoethanol (**3a**) and its sulfate monoester (**3b**).[8]

Results and Discussion

Thiocarbamoylation of Hydrazinoethanol (3a) and Hydrazinoethyl Hydrogen Sulfate (3b).—The reaction of **3a** with an equimolar amount of phenyl isothiocyanate in dioxane occurs at the substituted nitrogen atom producing **4** in 86% yield. In the presence of a molar excess of reagent **3a** is converted into the N,N′-bis(thiocarbamoyl) derivative **5** in 80% yield.



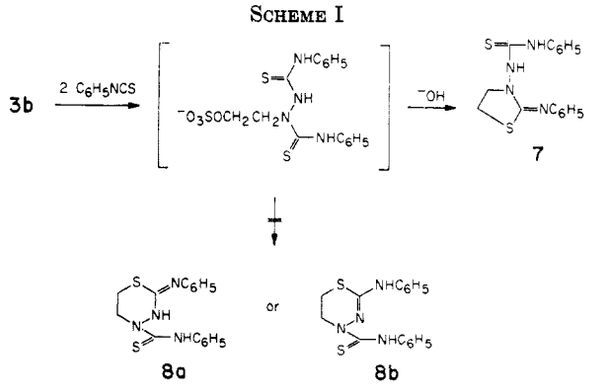
Equimolar amounts of hydrazinoethyl hydrogen sulfate (**3b**) and phenyl isothiocyanate are allowed to react in aqueous dioxane in the presence of an equivalent quantity of sodium hydroxide. When the crude derivative is isolated and treated with 1 *N* sodium hydroxide, 3-amino-2-(phenylimino) thiazolidine (**6**) is



obtained in 30% yield as the only cyclic product. In its high resolution mass spectrum, major fragments, $C_9H_{10}N_2S^+$ and $C_9H_9N_2S^+$, corresponding to loss of NH and NH_2 from the molecular ion, are consistent with the five-membered heterocyclic structure. Compound **6** is also obtained in 26% yield by warming **4** overnight in concentrated hydrochloric acid.

Treatment of **3b** with a molar or greater excess of phenyl isothiocyanate in alkaline aqueous dioxane (pH 8.5–9.0), followed by warming overnight at 40°, produces 3-(N-phenylthiocarbamoylamino)-2-(phenylimino)thiazolidine (**7**) in 38% yield. Mass spectral and nmr data make it possible to distinguish between **7** and alternative structures **8a** and **8b** (Scheme I).

SCHEME I



(1) For the previous paper in this series, see E. Cherbuliez, O. Espejo, B. Willhalm, and J. Rabinowitz, *Helv. Chim. Acta*, **51**, 241 (1968).

(2) National Academy of Sciences–National Aeronautics and Space Administration-Senior Research Associate.

(3) E. Cherbuliez, Br. Baehler, H. Jindra, G. Weber, G. Wyss, and J. Rabinowitz, *ibid.*, **48**, 1069 (1965).

(4) E. Cherbuliez, Br. Baehler, S. Jaccard, H. Jindra, G. Weber, G. Wyss, and J. Rabinowitz, *ibid.*, **49**, 807 (1966).

(5) E. Cherbuliez, Br. Baehler, O. Espejo, S. Jaccard, H. Jindra, and J. Rabinowitz, *ibid.*, **49**, 2408 (1966).

(6) E. Cherbuliez, Br. Baehler, O. Espejo, H. Jindra, B. Willhalm, and J. Rabinowitz, *ibid.*, **50**, 334 (1966).

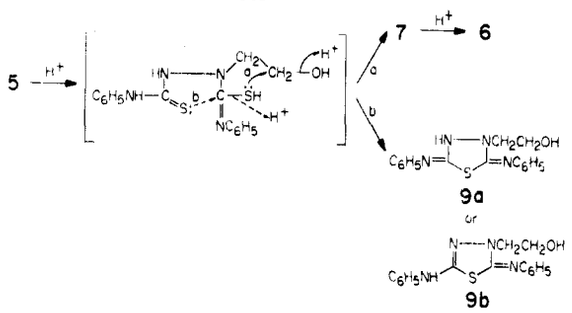
(7) E. Cherbuliez, S. Jaccard, H. Jindra, F. Tissot, and J. Rabinowitz, *ibid.*, **49**, 2400 (1966).

(8) E. Cherbuliez, O. Espejo, H. Jindra, and J. Rabinowitz, *ibid.*, **50**, 2019 (1967).

The nmr spectrum of **7** contains a two-proton, D_2O-exchangeable singlet at δ 9.86. The assignment of this singlet to the protons of the thiourea group is supported by the analogous assignment of a signal at δ 9.50 in the nmr spectrum of **5**. Protons bound to nitrogen in **8a** and **8b** would be expected to give rise to two singlets.[9] Furthermore, the high resolution mass spectrum of **7** contains major fragments, $C_9H_{10}N_2S^+$ and $C_9H_9N_2S^+$, which are difficult to reconcile with **8a** or **8b**, but are consistent with the proposed structure. These two fragments appear as major ions in the mass spectrum of **6**.

Two products are isolated after **5** (or the crude mixture resulting from reaction of **3a** with a molar excess of phenyl isothiocyanate) is heated overnight in concentrated hydrochloric acid. In addition to **6** obtained in 18% yield, a second compound obtained in 13% yield is assigned structure **9** (**a** or **b**, Scheme II).

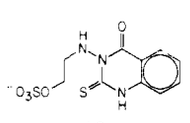
SCHEME II



A clearcut choice between the tautomeric structures cannot be made with available data.

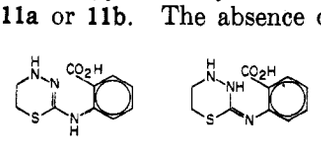
Acid-catalyzed cyclization of **5** apparently proceeds by two paths involving either one or the other sulfur atom (Scheme II). Either path a (displacement of water gives rise to **7** and ultimately **6** by hydrolysis of the thiocarbamoyl group) or path b (the displacement of hydrogen sulfide furnishes **9a** or **b**).

Treatment of **3b** with an equimolar amount of *o*-methoxycarbonylphenyl isothiocyanate yields a crude product whose infrared (ir) spectrum contains a broad band at 1675 cm^{-1}, which is suggestive of a 2-thiono-4-tetrahydroquinazolinone structure **10**.[10]



10

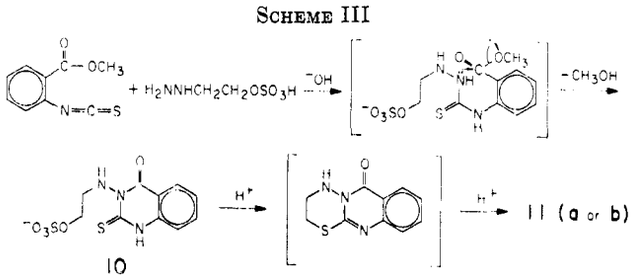
Refluxing the crude product overnight in hydrochloric acid converts it in 26% over-all yield into what appears to be either **11a** or **11b**. The absence of major fragments in the mass spectrum corresponding to loss of NH and NH_2 from the molecular ion, which was observed in the spectra of **6** and **7**, supports the six-membered heterocyclic structure. Of particular significance in the nmr spectrum is a triplet at δ 6.03 (J = 5.0 Hz) assigned to an amino proton adjacent to a methylene group. With the available data it is not possible to make a definite choice between structures **11a** and **11b**. However, the ultraviolet (uv) spectrum with maxima at 222 and 310 mμ is identical with that of 2-(*o*-carboxyphenylamino)-5,6-dihydro-4H-1,3-thiazine[10] and suggests the structure **11a** containing an endocyclic CN double bond.



11a **11b**

A probable pathway for formation of **11a** or **b** is presented in Scheme III. Thiocarbamoylation of **3b** at the unsubstituted nitrogen followed by intramolecular acylation produces **10**. Treatment of **10** with refluxing hydrochloric acid yields **11a** or **b** through ring closure and hydrolysis of the lactam function.

SCHEME III



Monothiocarbamoylation of hydrazinoethyl derivatives with phenyl isothiocyanate apparently takes place at the substituted nitrogen atom. Similar results have been reported for methyl- and isopropylhydrazine.[11] In direct contrast, the reaction of hydrazinoethyl sulfate (**3b**) with *o*-methoxycarbonylphenyl isothiocyanate involves the *un*substituted nitrogen atom. The probable and simplest explanation is that the proximity of the *o*-methoxycarbonyl to the isothiocyanate group may well cause sufficient steric crowding in the transition state for thiocarbamoylation that reaction at the unsubstituted nitrogen atom is preferred.[12]

Mono- and di-N,N alkylations of monosubstituted hydrazines (H_2NNHR) with organic halides and sulfates are known to take place at the substituted nitrogen atom. Only in the case of severe steric crowding (*e.g.*, triphenylmethylation of triphenylmethylhydrazine) is alkylation at the unsubstituted nitrogen atom preferred.[11] Acylation, however, is much more sensitive to steric effects. Reactions with anhydrides occur primarily at the substituted nitrogen atom, whereas reactions with esters and acid chlorides take place at either or both nitrogen atoms.[11] These observations, coupled with our results, suggest that the sensitivity to steric crowding in the transition state for thiocarbamoylation lies between those for alkylation and acylation.

Phenylcarbamoylation of Hydrazinoethanol (3a) and Hydrazinoethyl Hydrogen Sulfate (3b).—The reaction of **3a** with an equimolar amount of phenyl isocyanate

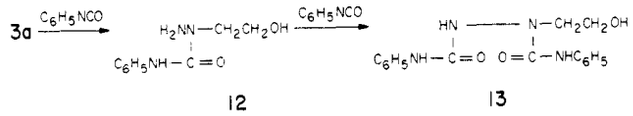
(9) The proton on the amino nitrogen of **8a** and **8b** would be expected to appear at higher field (δ < 9.0) since a similar proton in **9** appears at δ 8.25.

(10) E. Cherbuliez, B. Willhalm, O. Espejo, S. Jaccard, and J. Rabinowitz, *Helv. Chim. Acta*, **50**, 1440 (1967).

(11) P. A. S. Smith, "Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York-Amsterdam, 1966, Chapter 9, pp 119–201.

(12) Acylation of hydrazinoethanol (**3a**) with methyl benzoate required elevated temperatures, thus excluding the possibility of an initial acylation of **3b** with *o*-methoxycarbonylphenyl isothiocyanate.

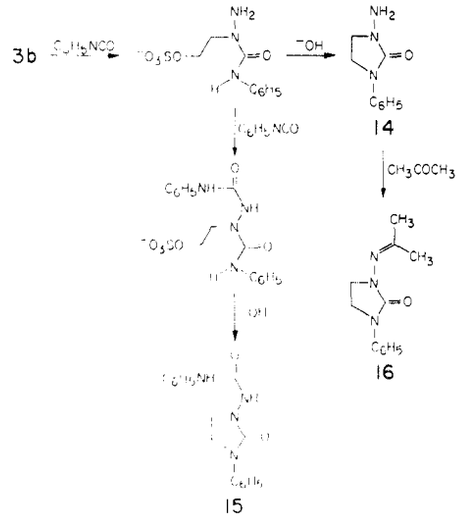
in dioxane produces **12** in 79% yield. Reaction with a molar excess of reagent furnishes **13** in 90% yield.



12 **13**

Reactions of **3b** with varying amounts of phenyl isocyanate are carried out in aqueous dioxane containing an amount of sodium hydroxide equivalent to that of **3b**. The crude carbamoyl sulfates, after treatment with 1 *N* sodium hydroxide, furnish mixtures of 3-amino-1-phenyl-2-imidazolidinone (**14**) and 3-(N-phenyl-carbamoylamino)-1-phenyl-2-imidazolidinone (**15**) as the major products in total yields ranging from 25 to 50% (Scheme IV).

SCHEME IV



15 **16**

The ir spectrum with carbonyl absorption at 1715 cm^{-1} and the high resolution mass spectrum with major fragments $C_9H_{10}N_2O^+$ and $C_9H_9N_2O^+$, corresponding to loss of NH and NH_2 from the molecular ion, are clearly characteristic of **14**. When acetone is used as a solvent in the isolation of **14**, the Schiff base 3-isopropylidenamino-1-phenyl-2-imidazolidinone (**16**) is obtained (Scheme IV).

Structure **15** is consistent with strong bands in its ir spectrum at 1720 and 1642 cm^{-1} which are characteristic of a carbonyl group in five-membered cyclic and open ureas, respectively.[13] Major fragments in the high resolution mass spectrum, $C_9H_{10}N_2O^+$ and $C_9H_9N_2O^+$, correspond to loss of C_6H_5NHCON and $C_6H_5NHCONH$ from the molecular ion or NH and NH_2 from the most abundant ion $C_9H_{11}N_3O^+$.

The reaction between equimolar quantities of **3b** and phenyl isocyanate followed by cyclization of the crude product furnishes a 50% combined yield of **14** and **15**, in which **15** comprises 15% of the total mixture. Apparently, the reaction of the monophenylcarbamoyl derivative of **3b** with a second molecule of reagent at the unsubstituted nitrogen atom can compete with monophenylcarbamoylation of unreacted **3b** at the substituted nitrogen atom. Phenylcarbamoylation of **3b** somehow enhances the reactivity of the unsubstituted nitrogen atom to phenyl isocyanate.

Exclusive N,N′ diderivatization using large excesses of phenyl isocyanate cannot be achieved owing to facile reaction of the reagent with water. Mixtures of **14** and **15** are produced with **15** predominating.

Like monophenylthiocarbamoylation, monophenylcarbamoylation of hydrazinoethyl derivatives takes place at the substituted nitrogen atom. These observations are similar to those made in reactions of methyl and isopropyl hydrazine with phenyl isocyanate and cyanic acid.[11]

Experimental Section

Materials.—Hydrazinoethanol, phenyl isothiocyanate, and phenyl isocyanate were used as obtained commercially. Hydrazinoethyl hydrogen sulfate was prepared from equimolecular amounts of hydrazinoethanol and concentrated sulfuric acid.[8] *o*-Methoxycarbonylphenyl isothiocyanate was prepared from methyl anthranilate and thiophosgene.[14]

Spectroscopic Data.—Melting points are uncorrected. Ir spectra were measured on a Perkin-Elmer 521 grating ir spectrometer. Uv spectra were obtained on a Cary 14 recording spectrophotometer. Unless otherwise specified, nmr spectra were recorded with an HR-100 Varian spectrometer with dimethyl sulfoxide-d_6 as solvent and capillary tetramethylsilane as internal standard. All mass spectra were obtained on a Consolidated Electrodynamics Corp. Model 21-110B high resolution mass spectrograph.[15]

Thiocarbamoylation of Hydrazinoethanol (3a) and Hydrazinoethyl Hydrogen Sulfate (3b). N-Phenyl-N′-hydroxyethyl-N′-aminothiourea (4).—A solution of 13.5 g (0.1 mol) of phenyl isothiocyanate in 30 ml of dioxane was added to 7.6 g (0.1 mol) of hydrazinoethanol in 50 ml of dioxane and stirred overnight at 30°. The dioxane was evaporated and the residue was stirred with 75 ml of anhydrous ether to bring about crystallization. The solid was filtered and dried under vacuum. The filtrate was evaporated to dryness and treated again with ether, affording a second crop of material for a total of 18.2 g (86%) of the thiourea **4**: mp 84–85°; ir (KBr) 3220 (NH) and 3340 cm^{-1} (OH); nmr δ 10.00 (s, 1, **NH**), 7.27 (m, 5, C_6H_5), 5.04 (s, 2, NH_2), 4.78 (t, 1, J = 5.0 Hz, CH_2OH), 4.06 (t, 2, J = 5.7 Hz, CH_2N), 3.70 ppm (t, 2, J = 5.9 Hz, CH_2O); mass spectrum[15] (70 eV)—211 (6.5), 193 (0.8), 177 (1.0), 167 (2.5), 135 (100) 119 (1.1), 103 (7.3), 93 (17), 77 (74).

Anal. Calcd for $C_9H_{13}N_3OS$: C, 51.10; H, 6.18; N, 19.8; S, 15.2. Found: C, 51.10; H, 6.43; N, 19.7; S, 15.1.

N,N′-Bis(phenylthiocarbamoyl)hydrazinoethanol (5).—Solutions of 13.5 g (0.1 mol) of phenyl isothiocyanate in 30 ml of dioxane and 3.8 g (0.05 mol) of hydrazinoethanol in 50 ml of dioxane were treated as in the preparation of **4** to yield 13.8 g (80%) of **5**: mp 114–117°; ir (KBr) 3230 (NH) and 3350 cm^{-1} (OH); nmr δ 10.03 (s, 1, **NH**), 9.62 (s, 1, **NH**), 9.50 (s, 1, **NH**), 7.31 (m, 10; $2C_6H_5$), 4.30 (s, 1, **OH**), and 3.68 ppm (m, 4, NCH_2CH_2O); mass spectrum[15] (70 ev)—the molecular ion could not be observed even under mildest volatilization conditions (temperature of sample <140°) because of the elimination of H_2S and the formation of compound **9a** or **b**, the resulting spectrum being identical in every respect with that of **9a** or **b**.

Anal. Calcd for $C_{16}H_{18}N_4OS_2$: C, 55.20; H, 5.23; N, 16.2; S, 18.5. Found: C, 55.60; H, 5.54; N, 16.4; S, 17.7.

3-Amino-2-(phenylimino)thiazolidine (6). A. From Treatment of 4 with Concentrated Hydrochloric Acid.—A solution of 2.11 g (0.01 mol) of **4** in 15 ml of concentrated hydrochloric acid was

(13) K. Nakanishi, "Infrared Absorption Spectroscopy-Practical," Holden-Day, Inc., San Francisco, Calif., and Nankodo Co., Ltd., Tokyo, 1962, p 116.

(14) J. C. Howard and G. Klein, *J. Org. Chem.*, **27**, 3701 (1962).

(15) Accurate mass determinations were made from measurements of line positions on ion-detecting photoplates. Relative ion abundance was measured from low resolution scans with an electron multiplier detector. Where elemental compositions are not reported, only the low resolution spectrum was obtained. For high resolution spectra, we list, in addition to the composition and relative intensity, the difference in millimass units between the found mass and the exact mass calculated for an ion of the listed composition. As an example, the molecular ion of **14** has the composition $C_9H_{11}N_3O$ and is the most intense peak in the spectrum; its found mass exceeds that of the calculated mass by 0.5 millimass units; thus, this ion is reported as $C_9H_{11}N_3O$ (100) 0.5. In general, we list the most abundant ion in each 14-mass unit interval ($2 + 14n <$ nominal mass $\leq 16 + 14n$).

heated overnight (100°), diluted with water to 60 ml, filtered, and neutralized with concentrated sodium hydroxide in an ice bath. The oil that separated was washed with cold water and dissolved in a few drops of methanol. Water was added until turbidity persisted. In a few days, 0.5 g (26%) of crystalline **6** was obtained: mp 86–88z; ir (KBr) 1618 (C=N) and 3420 and 3280 cm^{-1} (NH_2); uv max 250 mμ (ε 9980); nmr δ 7.08 (m, 5, C_6H_5) 4.66 (s 2, NH_2), 3.54 (t, 2, J = 7.0 Hz, CH_2N), and 3.10 ppm (t, 2, J = 7.0 Hz, CH_2S); mass spectrum[15] (70 eV)—$C_9H_{11}N_3S$ (85) 0.0, $C_9H_{10}N_2S$ (2.7) −1.3, $C_9H_9N_2S$ (3.0) −0.4, $C_7H_7N_3$ (2.0) 0.5, $C_8H_8N_3$ (5.5) 0.0, C_7H_5NS (27) −0.8, $C_7H_6N_2$ (5.1) −0.2, C_7H_6N (16) −0.8, C_6H_5N (5.5) 0.1, C_6H_5 (100) 0.8.

Anal. Calcd for $C_9H_{11}N_3S$: C, 56.0; H, 5.75; N, 21.8; S, 16.6. Found: C, 55.9; H, 5.74; N, 21.2; S, 16.0.

B. From Treatment of the Monophenylthiocarbamoyl Derivative of 3b with 1 *N* Sodium Hydroxide.—To a solution of 1.42 g (0.01 mol) of **3b** in 40 ml of 50% aqueous dioxane adjusted to pH 8.5–9.0 with 1 *N* sodium hydroxide was added 1.35 g (0.01 mol) of phenyl isothiocyanate in 10 ml of dioxane. The pH was maintained at 8.5–9.0 by the addition of 1 *N* sodium hydroxide to a total of 10 ml (including the amount added initially). After stirring overnight, the solution was evaporated to dryness. The phenylthiocarbamoyl derivative of **5b** was dissolved in methanol and filtered. The filtrate was again evaporated to dryness and the residue was washed with ether, dried, and stirred with 20 ml of 1 *N* sodium hydroxide. The precipitate was collected after a few hours, washed with a small quantity of cold water, and dried yielding 0.5 g (26%) of **6**. Additional material (0.2 to 0.3 g) may be obtained by extracting the aqueous alkaline solution with chloroform.

3-(N-Phenylthiocarbamoylamino)-2-(phenylimino)thiazolidine (7).—To a solution of 1.92 (0.01 mol) **3b** in 30 ml of water and 20 ml of dioxane at pH 8.5–9.0 was added a solution of 5.4 g (0.04 mole) of phenyl isothiocyanate in 20 ml of dioxane with the pH maintained by the simultaneous addition of 1 *N* sodium hydroxide. After addition of the isothiocyanate and at least 20 ml of the base, the temperature was raised to 40°. The pH was adjusted if necessary and the reaction continued overnight. Dilution with 40 ml of water afforded a precipitate which after recrystallization from methanol yielded 1.25 g (38%) of **7**: mp 205–206°; ir (KBr) 1600 (C=N) and 3150 cm^{-1} (NH); uv max (95% C_2H_5OH) 250 mμ (ε 27,200); nmr δ 9.86 (s, 2, HNCSNH), 7.44 (m, 10, 2 C_6H_5), 4.15 (t, 2, J = 7.0 Hz, CH_2N), and 3.85 ppm (t, 2, J = 7.0 Hz, CH_2S); mass spectrum[15] (70 eV)—328 (0.8), 295 (3.2) 261 (0.9) 236 (1.1), 218 (1.0), 210 (0.9), $C_9H_{11}N_3S$ (21) −0.4 $C_9H_{10}N_2S$ (3.7) −0.4, $C_9H_9N_2S$ (4.6) 0.7, 162 (1.7), C_8H_7NS (2.4) 0.0, C_7H_5NS (62) −0.4, $C_7H_6N_2$ (6.2) −0.5, C_7H_3N (14) 0.2, C_6H_7N (27) 0.1, C_6H_5 (100) −0.6.

Anal. Calcd for $C_{15}H_{16}N_4S_2$: C, 58.5; H, 4.91; N, 17.0; S, 19.6. Found: C, 58.5; H, 5.11; N, 16.8; S, 19.4.

2,5-Diphenylimino-3-hydroxyethyl-1,3,4-thiadiazolidine (9a).—Solutions of 0.76 g (0.01 mol) of hydrazinoethanol (**3a**) in 20 ml of dioxane and 2.7 g (0.02 mol) of phenyl isothiocyanate in 20 ml of dioxane were slowly mixed at room temperature and stirred overnight. The solvent was evaporated and the residue (crude **5**) was heated (100°) overnight with 40 ml of concentrated hydrochloric acid. (Alternatively, **5** can be treated directly with concentrated acid, but it is not necessary to isolate pure **5** to convert it into **9a** or **b**.) Dilution of the reaction mixture to 200 ml with water yielded a precipitate which after recrystallization in boiling ethanol furnished 0.4 g (13%) of **9a** or **b**: mp 164–165°; ir (KBr) 1618 (C=N), 1600 (C=N), 3300 (OH), and 3140 cm^{-1} (NH); uv max (95% C_2H_5OH) 232 mμ (ε 16,300) and 257 (19,750); nmr δ 8.25 (s, 1, NH), 7.40 (m, 10, $2C_6H_5$), 4.72 (t, 1, J = 5.7 Hz; CH_2OH), 4.03 (t, 2, J = 6.0 Hz, CH_2N), 3.69 ppm (t, 2, J = 6.0 Hz; CH_2O); mass spectrum[15] (70 eV)—$C_{16}H_{16}N_4OS$ (9.8) 0.7, $C_{16}H_{14}N_4S$ (0.7) 2.3, $C_{15}H_{13}N_4S$ (0.6) −0.5, $C_{14}H_{12}N_4S$ (24) 1.2 $C_{14}H_{10}N_3S$ (0.4) −1.0, $C_{14}H_{11}N_4$ (2.5) 0.5, $C_{13}H_{10}N_3$ (1.7) 0.2, $C_{13}H_{11}N_2$ (3.9) −1.4, $C_{13}H_8N$ (2.2) −0.8, $C_{12}H_9N$ (1.4) 0.5, $C_7H_5N_2S$ (2.9) 1.2, $C_8H_8N_3$ (2.2), 0.2, C_7H_6NS (8.0) −0.5, $C_7H_6N_2$ (29) 0.1, C_7H_6N (12) 0.3, C_6H_6N (13) −1.0, C_6H_5 (100) 0.0.

Anal. Calcd for $C_{16}H_{16}N_4OS$: C, 61.3; H, 5.20; N, 17.9; S, 10.3. Found: C, 61.3; H, 5.40; N, 17.6; S, 11.1.

When the aqueous filtrate above was neutralized with concentrated sodium hydroxide and cooled an oil was formed. The oil was washed several times with cold water, dissolved in methanol, and filtered. Water was added until turbidity persisted. Precipitation of 0.3 g (16%) of **6** occurred in a few days.

2-(*o*-Carboxyphenylamino)-5,6-dihydro-4H-1,3,4-thiadiazine (11a).—Solutions of 3.84 g (0.02 mol) of **3b** in 100 ml of 50% aqueous dioxane (pH 8.5–9.0) and of 3.95 g (0.02 mol) of *o*-methoxycarbonylphenyl isothiocyanate in 10 ml of dioxane were treated as in synthesis B of **6**. The residue [ir (KBr) 1675 cm^{-1} (C=O)] obtained after evaporation of the aqueous dioxane was refluxed overnight in 100 ml of 1 *N* hydrochloric acid. The mixture was evaporated to dryness, the residue was neutralized with 2 *N* sodium hydroxide, and the alkaline solution was filtered. When the filtrate was acidified with hydrochloric acid, a pasty precipitate formed which after crystallization from 50 ml of hot methanol yielded 0.62 g (26%) of **11a** or **b**: mp 185–186°; ir (KBr) 1660 (C=N) 1720, (C=O), 3310 (NH), and 3450 cm^{-1} (OH); uv max (95% C_2H_5OH) 222 mμ (ε 59,100) and 311 (4850); nmr δ 11.52 (s, 1, CO_2H or NH), 7.60 (m, 4, C_6H_4), 6.03 (t, 1, J = 5.0 Hz, $NHCH_2$), 3.30 (s, 1, CO_2H or NH and HDO), 3.11 (t, 2, J = 6.5 Hz, CH_2N), and 2.90 ppm (t, 2, J = 6.5 Hz, CH_2S); mass spectrum[15] (70 eV)—$C_{10}H_{11}N_3O_2S$ (1.0) 0.9, $C_{10}H_9N_3O_2$ (0.9) 0.4, $C_9H_8N_3O_2$ (38) −0.4, $C_8H_7N_3O_2$ (6.7) −0.1, $C_8H_7N_2O_2$ (100) 0.4, $C_8H_4NO_2$ (68) −0.5, $C_7H_5N_2O$ (1.7) 0.3, C_7H_5NO (34) −0.8, C_6H_4NO (3.1) −0.7, C_6H_4O (33) −0.4, C_2H_6NS (7.7) −1.3.

Anal. Calcd for $C_{10}H_{11}N_3O_2S$: C, 50.7; H, 4.65; N, 17.7; S, 13.5. Found: C, 50.9; H, 4.59; H, 17.2; S, 13.0.

Phenylcarbamoylation of Hydrazinoethanol (3a) and Hydrazinoethyl Hydrogen Sulfate (3b). N-Phenyl-N′-hydroxyethyl-N′-aminourea (12).—A solution of 2.38 g (0.02 mol) of phenyl isocyanate in 20 ml of dioxane was added to 1.52 g (0.02 mol) **5a** dissolved in 20 ml of dioxane and stirred overnight. The solvent was evaporated and the residue was dissolved in a minimum amount of acetone. The crystalline product obtained upon addition of anhydrous ether was removed by filtration and the filtrate was evaporated to dryness. A second crop of crystals was obtained when the residue was treated as before, bringing the total yield of **12** to 3.10 g (79%): mp 112–113°; ir (KBr 1645 (C=O), 3310 (NH), and 3400 cm^{-1} (OH); nmr δ 8.90 (s, 1, NH), 7.20 (m, 5, C_6H_5), 4.65 (s, 2, NH_2), 4.60 (t, 1, J = 5.0 Hz, CH_2OH), and 3.50 ppm (m, 4, NCH_2CH_2O); mass spectrum[15] (70 eV)—$C_9H_{13}N_3O_2$ (18) −0.5, C_7H_5O (13) −0.9, C_6H_7N (6.9) −0.5, $C_2H_5N_2O$ (55) −0.4, C_5H_5 (6.7) −0.7, CH_5N_2 (100) −0.3.

Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.2; H, 6.72; N, 21.6. Found: C, 55.6; H, 6.73; N, 21.7.

N,N′-Bis(phenylcarbamoyl)hydrazinoethanol (13).—A solution of 7.14 g (0.06 mol) of phenyl isocyanate in 40 ml of dioxane was added to 2.28 g (0.03 mol) of **3a** dissolved in 20 ml of dioxane and stirred overnight. The solution was concentrated and anhydrous ether was added to cause precipitation of **13**. A second crop was obtained by reducing the volume and adding ether as before, bringing the total yield of **13** to 8.5 g (90%): mp 180–182°; ir (KBr) 1670 (C=O), 1657 (C=O), 3300 (NH), and 3400 cm^{-1} (OH); nmr δ 8.92 (s, 1, NH), 8.78 (s, 1, NH), 8.10 (s, 1, NH), 7.17 (m, 10, $2C_6H_5$), 4.80 (t, 1, J = 5.0 Hz, CH_2OH), and 3.48 ppm (m, 4, NCH_2CH_2O); mass spectrum[15] (70 ev)—$C_{16}H_{18}N_4O_3$ (3.1) −1.7, $C_{10}H_{11}N_3O_3$ (2.8) −0.6, $C_{10}H_9N_3O_2$ (0.8) −1.1, $C_9H_{13}N_3O_2$ (9.5) −1.6 $C_9H_{11}N_3O$ (10) 0.5, $C_8H_{10}N_3O$ (13) −0.7, $C_7H_8N_2$ (3.0) −0.5, C_7H_5NO (65) −1.0, C_7H_7N (2.0) −0.1, C_6H_7N (100) −1.3, C_6H_5 (35) −1.3.

Anal. Calcd for $C_{16}H_{18}N_4O_3$: C, 61.0; H, 5.78; N, 17.8. Found: C, 61.5; H, 5.84; N, 17.5.

3-Amino-1-phenyl-2-imidazolidinone (14) and 3-(N-Phenylcarbamoylamino)-1-phenyl-2-imidazolidinone (15).—A solution of 1.92 g (0.01 mol) of **3b** in 3–4 ml of water was brought to pH 8.5–9.0 with 10 ml of 1 *N* sodium hydroxide and diluted with 13 ml of dioxane. A solution of 1.19 g (0.01 mol) of phenyl isocyanate in 10 ml of dioxane was added and stirred for 5 hr. The reaction mixture was then diluted to 75 ml with water and allowed to stir an additional 1 hr. Diphenylurea (0.151 g, 0.8 mmol) was removed by filtration and the filtrate was extracted twice with 30-ml portions of chloroform. The aqueous solution was evaporated giving carbamoylated sodium hydrazinoethyl sulfate as an amorphous, hygroscopic solid. The crude salt was dissolved in 25 ml of 1 *N* sodium hydroxide and warmed 3 hr at 55° during which time gas evolved and a solid precipitated. The solid was filtered and the filtrate (A) was set aside. According to tlc on silica gel G_f (methylene chloride:methanol, 24:1), the solid consisted of only two components. The solid was dissolved in hot methanol, filtered, and cooled, producing 0.223 g (8%) (based on **3b**) of **15**: mp 254–256° dec; ir (KBr) 1720 (cyclic C=O), 1642 (C=O), and 3310 cm^{-1} (NH); uv max (CH_3OH) 242 mμ (ε 2900), and 270 and 280 (shoulders); nmr δ 8.76

(s, 1, NH), 8.24 (s, 1, NH), 7.22 (m, 10, $2C_6H_5$), and 3.56 ppm (m, 4, NCH_2CH_2N); mass spectrum[15] (70 eV)—$C_{16}H_{16}N_4O_2$ (3.3) 0.2, $C_{10}H_9N_3O_2$ (7.8) 0.2, $C_9H_{11}N_3O$ (100) −1.1, $C_9H_{10}N_2O$ (17) −0.2, $C_9H_9N_2O$ (2.4) −0.2, $C_8H_{10}N_3$ (1.8) 0.2, $C_8H_7N_2$ (3.7) −1.3, C_7H_5NO (71) 0.0, C_7H_8N (27) −1.5, C_6H_5N (34) −0.8, C_6H_5 (30) −1.5.

Anal. Calcd for $C_{16}H_{16}N_4O_2$: C, 64.9; H, 5.43; N, 18.9. Found: C, 64.7; H, 5.38; N, 19.2.

The mother liquors (B) from crystallization of **15** were evaporated to dryness; the resulting solid was redissolved in a minimum of cold chloroform and preparatively chromatographed as above. The major band (R_f 0.31) was eluted from the plates with methanol in the usual manner yielding 0.213 g of **14**, mp 120–122°.

The basic aqueous filtrate above (A) was extracted twice with 25 ml of chloroform. After drying (anhydrous sodium sulfate) and filtering, the chloroform extract was evaporated to dryness. The residue was recrystallized from chloroform–hexane, yielding 0.530 g of **14**. The total yield of **14** from A and B was 0.743 g (42%): mp 120–122°; ir (KBr) 1715 (C=O) and 3350 cm^{-1} (NH_2); uv max (CH_3OH) 246 mμ (ε 18,500); nmr ($DCCl_3$) δ 7.33 (m, 5, C_6H_5), 4.00 (s, 2, NH_2), and 3.62 ppm (m, 4, NCH_2CH_2N); mass spectrum[15] (70 eV)—$C_9H_{11}N_3O$ (100) 0.5, $C_9H_{10}N_2O$ (4.3) −1.0, $C_9H_9N_2O$ (4.8) −4.0, $C_7H_8N_2$ (3.2) 0.0, C_7H_8NO (18) −0.3, C_7H_7N (30) −0.1, C_6H_5N (23) −0.5, C_6H_5 (90) −1.3.

Anal. Calcd for $C_9H_{11}N_3O$: C, 61.0; H, 6.26; N, 23.7. Found: C, 60.7; H, 6.32; N, 22.2.

3-Isopropylidenamino-1-phenyl-2-imidazolidinone (16). A.—In a separate experiment involving equimolar amounts of phenylisocyanate and hydrazinoethyl hydrogen sulfate executed as above, mother liquors (B) were evaporated to dryness and the residue was dissolved in acetone and chromatographed as above, giving rise to several bands. Eluting the major band with acetone and evaporating the solvent produces a solid that, after recrystallization from carbon tetrachloride–hexane, afforded 0.221 g (10%) of **16**: mp 54–56°; ir (KBr) 1725 (C=O) and 1650 cm^{-1} (C=N); uv max (CH_3OH) 248 mμ (ε 4500); nmr (CCl_4) δ 7.16 (m, 5, C_6H_5), 3.52 (s, 4, NCH_2CH_2N), 1.84 (s, 3, CH_3), and 1.96 ppm (s, 3, CH_3); mass spectrum[15] (70 ev)—217 (100), 202 (7.8), 175 (27), 161 (7.3), 147 (6.9), 133 (4.7), 118 (34), 106 (61), 91 (47), 77 (64).

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.3; H, 6.96; N, 19.3. Found: C, 66.6; H, 6.89; N, 19.3.

B.—In 2 ml of acetone 51 mg (0.3 mmol) of **14** was dissolved and allowed to stand for 1.5 hr. The acetone was removed and the residue was dissolved in chloroform. Preparative tlc of the mixture yielded 23 mg (40%) of **16**.

Registry No.—Phenyl isocyanate, 103-71-9; **3a**, 109-84-2; **3b**, 3657-48-5; **4**, 18339-72-5; **5**, 18339-61-2; **6**, 18339-62-3; **7**, 18339-63-4; **9a**, 18339-64-5; **11a**, 18339-65-6; **12**, 18339-66-7; **13**, 18339-67-8; **14**, 18339-68-9; **15**, 18339-69-0; **16**, 18339-70-3.

Acknowledgment.—The authors wish to thank Dr. Emile Cherbuliez, Honorary Professor at the University of Geneva (Switzerland), for reviewing the manuscript.

A New Synthesis of 5-Acyl-2-oxazolin-4-ones and of β-Keto-α-hydroxy Acid Amides from the Reaction of 2,2,2-Trialkoxy-2,2-dihydro-1,3,2-dioxaphospholenes with Acylisocyanates

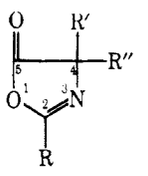
FAUSTO RAMIREZ[1] AND C. DAVID TELEFUS

Department of Chemistry of the State University of New York at Stony Brook, Stony Brook, New York 11790

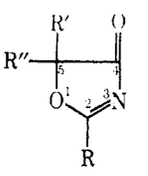
Received August 26, 1968

A new reaction leading to 5-acyl-2-oxazolin-4-ones and to the corresponding hydrolysis products, β-keto-α-hydroxy acid amides, is described. The reaction involves two steps: (1) the formation of a 2,2,2-trialkoxy-2,2-dihydro-1,3,2-dioxaphospholene from a trialkyl phosphite and an α-dicarbonyl compound and (2) the reaction of the phospholene with an acylisocyanate to yield the oxazolone and a trialkyl phosphate.

The 2-oxazolin-5-ones ("5-oxazolones" or azlactones[2]) (**1**) have been extensively investigated because of their application in the synthesis of α-amino acids. However, the 2-oxazolin-4-ones (**2**) have received little attention,[3-7] in spite of their potential use in the synthesis of α-hydroxy acid amides.



1



2

This paper describes a new reaction whose net effect is to convert an α-dicarbonyl compound (**3**) and an acylisocyanate[8,9] (**4**) into a 5-acyl-2-oxazolin-4-one (**6**), the precursor of a β-keto-α-hydroxy acid amide (**8**). The reagent employed in this reductive condensation is a trialkyl phosphite (**5**), which is first combined with the α-dicarbonyl compound to form a 2,2,2-trialkoxy-2,2-dihydro-1,3,2-dioxaphospholene.[10] Reac-

(1) John Simon Guggenheim Fellow, 1968. This work was supported by Grants from the U. S. Public Health Service (CA-04769), the National Science Foundation (GP-6690), and the Petroleum Research Fund of the American Chemical Society (3082).

(2) (a) H. E. Carter in "Organic Reactions," Vol. 3, R. Adams, Ed., John Wiley & Sons, Inc., New York, N. Y., 1946; (b) F. Korte and K. Heinz Buckel, *Chem. Ber.*, **93**, 104 (1960).

(3) (a) F. R. Japp and A. Findlay, *J. Chem. Soc.*, **75**, 1028 (1899); (b) C. F. Howell, N. R. Quinones and R. A. Hardy, *J. Org. Chem.*, **27**, 1679 (1962).

(4) (a) I. V. Smolanka, S. M. Khripak, and V. I. Staninets, *Ukr. Khim. Zh.*, **30** (3), 265 (1964); (b) H. Najer, R. Giudicelli, and J. Menin, *Bull. Soc. Chim. Fr.*, **8–9**, 1810 (1963).

(5) K. Hohenlohe-Oehringen, *Monatsh. Chem.*, **89**, 588 (1958).

(6) (a) J. C. Sheehan and P. T. Izzo, *J. Amer. Chem. Soc.*, **71**, 4059 (1949); (b) R. Neidlein, *Arch. Pharm.*, **298** (2), 124 (1965).

(7) (a) R. Filler, *Advan. Heterocycl. Chem.*, **4**, 71 (1965); (b) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957.

(8) (a) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28**, 1805 (1963); (b) O. Billeter, *Ber.*, **36**, 3218 (1903).

(9) P. A. S. Smith, "The Chemistry of Open-chain Organic Nitrogen Compounds," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 6.

(10) The literature has been reviewed: (a) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968); (b) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964).