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Urethans of 2-Mercaptoethanol

BY J. F. SMITH AND E. C. FRIEDRICH

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The direction of addition of one mole of isocyanate to 2-mercaptoethanol is determined by the type of catalysis used. Basic catalysts lead to a series of S-urethans; uncatalyzed or acid-catalyzed reactions afford the corresponding series of O-urethans. The O-urethans of 2-mercaptoethanol polymerize rapidly under the influence of aqueous alkali to give polysulfides of general formula $ArNHCOO(CH_2CH_2S)_nH$.

The reaction between an isocyanate and a compound containing active hydrogen is generally considered[1] to take place by attack at the electrophilic carbon atom of the isocyanate group. The relative rates of reaction of different compounds with isocyanates thus depend on the nucleophilicity of the reactive center in the attacking compound, neglecting steric and other considerations.

This generalization is amply supported by kinetic evidence where the differences in nucleophilicity are clear cut; for instance, in the absence of catalysts, alcohols react more rapidly with isocyanates than the less nucleophilic thiols.[2] The mercaptide ion, however, as distinct from the thiol group, is very strongly nucleophilic, more so than the alkoxide ion, and under reaction conditions which might tend to favor ionization it is not easy to predict which of the two groups, alcohol or mercaptan, would react the faster with isocyanate.

Dyer and Glenn[3] have shown that tertiary amines have an extremely pronounced catalytic effect on the reaction rate of thiols with isocyanates. Basic catalysis of the alcohol/isocyanate reaction also occurs. Such catalysts would be expected to favor the formation of mercaptide and alkoxide ions, respectively, as intermediates but not necessarily to the same extent. It was of interest therefore to determine the relative reactivities of thiols and alcohols both in the presence and the absence of catalysts. The reaction of 2-mercaptoethanol with one molar equivalent of isocyanate affords an interesting opportunity to study these reactions in direct competition.

Bennett and Whincop[4] first studied the addition of phenyl isocyanate to 2-mercaptoethanol. They obtained a product of m.p. 59–60° to which they assigned the structure (I, R = C_6H_5) on the grounds that it showed no mercaptan properties. The preparation of I from this uncatalyzed reaction seemed unlikely in view of the predictions of Arnold, *et al.*,[1] and the experiments of Bennett and Whincop have been repeated. Our product had m.p. 61–62°, close to that of Bennett and Whincop,[4] but was shown to be the O-urethan II (R = C_6H_5) by the preparation of thiol derivatives and by oxidation to a disulfide (III, R = C_6H_5) identical with the reaction product of phenyl isocyanate with dithiodiethanol (IV).

The specificity of the reaction was demonstrated by the fact that no diminution in the titrated mercaptan content of the mixture occurred when phenyl isocyanate was allowed to react with mercaptoethanol.

$$\begin{tikzcd}
RNCO + HOCH_2CH_2SH \arrow[r] \arrow[d, "\text{oxidn.}"] & \underset{(I)}{RNHCOSCH_2CH_2OH} \arrow[d, "RNCO"] \\
\underset{(IV)}{HOCH_2CH_2SSCH_2CH_2OH} \arrow[d] & \underset{(V)}{RNHCOSCH_2CH_2OCONHR} \\
\underset{(III)}{RNHCOOCH_2CH_2SSCH_2CH_2OCONHR} & \underset{(II)}{RNHCOOCH_2CH_2SH} \arrow[l, "\text{oxidn.}"'] \arrow[u, "RNCO"']
\end{tikzcd}$$

In the absence of catalysts, then, reaction with hydroxyl was clearly preferred over that with thiol, confirming the predictions[1] based on electronic considerations. The use of basic catalysts completely altered the course of the reaction, however. Phenyl isocyanate reacted with 2-mercaptoethanol in the presence of *t*-amine catalysts to give a new product of m.p. 72–74° which depressed the m.p. of II (R = C_6H_5) but reacted with phenyl isocyanate to give the same bis-urethan (V, R = C_6H_5) and must therefore be the S-urethan (I, R = C_6H_5). Again, the specificity of the amine-catalyzed reaction was demonstrated by the disappearance of titrated mercaptan in the crude reaction product, emphasizing the extremely specific nature of amine catalysis toward the thiol group.

The generality of the reaction was confirmed by carrying out catalyzed and uncatalyzed reactions of 2-mercaptoethanol with one mole each of *p*-methoxyphenyl isocyanate and α-naphthyl isocyanate. In each case two series of urethans resulted: S-urethans from base-catalyzed reactions and O-urethans from uncatalyzed or acid-catalyzed reactions. The two series were differentiated by oxidation to disulfides of the O-urethans under conditions which left the S-urethans unchanged, and by slight but definite differences in their infrared absorption spectra, discussed below.

The carbonyl absorption bands of alkyl esters (5.72–5.76 μ)[5] and their thiol ester analogs (5.97 μ)[6] show well-defined differences in wave length. This difference was duplicated in the carbonyl absorption spectra of the S- and O-urethans of mercaptoethanol where it was sufficiently pronounced to be diagnostic of structure. The S-

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[1] R. G. Arnold, J. A. Nelson and J. J. Verbanc, *Chem. Revs.*, **57**, 49 (1957); J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 19 (1949).

[2] S. Petersen, *Ann.*, **562**, 205 (1949).

[3] E. Dyer and J. F. Glenn, THIS JOURNAL, **79**, 366 (1957).

[4] G. M. Bennett and E. M. Whincop, *J. Chem. Soc.*, **119**, 1861 (1921).

[5] H. W. Thompson and P. Torkington, *ibid.*, 640 (1945).

[6] R. S. Rasmussen and R. R. Brattain, "Chemistry of Penicillin," edited by H. T. Clarke, J. R. Johnson and Sir Robert Robinson, Princeton University Press, Princeton, N. J., 1949, p. 404.

urethan carbonyl absorption bands lay between 6.0 and 6.1 μ while the O-urethans absorbed between 5.8 and 6.0 μ. The carbonyl absorption bands of the phenylurethans of ethanol and ethyl mercaptan, prepared for comparison, were 5.80 and 6.05 μ, respectively. The bis-urethans of 2-mercaptoethanol all showed two bands, one falling within each wave length range.

The Action of Alkali on 2-Mercaptoethyl Carbamates.—During the examination of the lower melting reaction product (II, R = C_6H_5) of 2-mercaptoethanol and phenyl isocyanate, it was discovered that this compound and other 2-mercaptoethyl carbanilates polymerized rapidly under the influence of alkali to form a series of low-molecular weight polysulfides of the general formula (VI, n = 2–8). Aniline and carbon dioxide also were formed.

$$\underset{\text{II}}{n\text{RNHCOOCH}_2\text{CH}_2\text{SH}} \xrightarrow{\text{OH}^-} (n-1)\text{RNH}_2 + (n-1)\text{CO}_2 + \underset{\text{VI}}{\text{RNHCOO}(\text{CH}_2\text{CH}_2\text{S})_n\text{H}}$$

The structure (VI) of the polysulfides was assigned by elemental analysis and infrared spectra (carbonyl absorption band, 5.87 μ, within the range of O-urethans). The chain length varied within limits (n = 2–8) according to the reaction conditions used; chain termination by precipitation caused preparations in water to give short-chain products, while non-aqueous media of higher solvent power gave somewhat higher molecular weights. No products having higher molecular weights than about eight units were obtained presumably because of the extreme insolubility of the higher members of the series.

It is interesting to speculate on the mechanism of this reaction. It cannot be a simple hydrolysis of the urethan followed by polymerization of the mercaptoethanol released because it occurs rapidly in the cold by simple admixture of 2-mercaptoethyl carbanilate with dilute aqueous alkali, conditions which do not cause polymerization of 2-mercaptoethanol. Alternative possibilities involve either intramolecular elimination of carbanilate ion releasing ethylene sulfide which subsequently polymerizes, or direct nucleophilic attack by the mercaptide ion of one molecule at the methylene group adjacent to the ester link of another. The latter possibility also presupposes an unusual carbon–oxygen fission with the formation of a new carbon–sulfur bond and the release of carbanilate ion, a succession of such reactions leading to the build-up of the polymer chain.

The rapid polymerization of the O-urethan of 2-mercaptoethanol under the influence of alkali led to some difficulty in their characterization as mercaptans. It is possible that the lack of mercaptan properties ascribed by Bennett and Whincop[4] to the reaction product of phenyl isocyanate and 2-mercaptoethanol was due to an unnoticed change from the monomer II to the alkali-insoluble polysulfide under the conditions selected to test for the presence of thiol groups. For instance, the change occurred rapidly in the cold with no apparent dissolution and very little change in physical appearance, when the monomer II was stirred with aqueous alkali. In our work the oxidation to disulfides of 2-mercaptoethyl carbamates was carried out in acetone or methanol solution, using ferric chloride as oxidizing agent to avoid this difficulty.

Experimental

Infrared spectra were determined on Nujol mulls in a Perkin–Elmer model 21 double beam spectrophotometer.

Preparation of 2-Mercaptoethyl Carbamates. (a) **2-Mercaptoethyl Carbanilate.**—2-Mercaptoethanol (89 g., 1.14 moles) and phenyl isocyanate (136 g., 1.14 moles) were mixed together and cooled somewhat to moderate the vigorous reaction which ensued. The reaction mixture solidified overnight. Recrystallization from benzene gave white needles of 2-mercaptoethyl carbanilate (II, R = C_6H_5). m.p. 62° (lit.[4] gives m.p. 59–60° for the product from this reaction).

Anal. Calcd. for $C_9H_{11}NO_2S$: S, 16.2. Found: S, 15.9; as –SH[7] in crude product, 16.6; λ_{co} 5.87 μ.[8]

(b) **2-Mercaptoethyl *p*-methoxycarbanilate** (II, R = C_6H_4OMe), prepared from *p*-methoxyphenyl isocyanate (60 g., 4.03 moles) and 2-mercaptoethanol (31.2 g., 4.0 moles) in 300 ml. of dry benzene, had m.p. 76–77° after recrystallization from benzene.

Anal. Calcd. for $C_{10}H_{13}NSO_3$: C, 52.9; H, 5.7; S, 14.1. Found: C, 52.8; H, 5.7; S, 13.8; S (as –SH), 13.9; λ_{co}, 5.90 μ.

(c) **2-Mercaptoethyl 1-naphthylcarbamate** (II, R = $C_{10}H_7$), prepared from 1-naphthyl isocyanate (10 g., 0.069 mole) and 2-mercaptoethanol (5 g., 0.064 mole) in 50 ml. of benzene saturated with anhydrous hydrogen chloride, had m.p. 79–80° after recrystallization from benzene–ligroin.

Anal. Calcd. for $C_{13}H_{13}NSO_2$: C, 63.1; H, 5.3; S, 13.0. Found: C, 62.9; H, 5.3; S, 12.9; S (as –SH), 13.0; λ_{co}, 5.92 μ.

Preparation of 2-Hydroxyethyl Thiolcarbamates. (a) **2-Hydroxyethyl Thiolcarbanilate.**—A solution of 2-mercaptoethanol (22.4 g., 0.287 mole) in 150 ml. of benzene containing two drops of diethylcyclohexylamine was stirred and treated dropwise with phenyl isocyanate (30.1 g., 0.253 mole). After 24 hours the precipitate which separated was collected and recrystallized from benzene to give shiny plates of 2-hydroxyethyl thiolcarbanilate (I, R = C_6H_5). m.p. 72–74° (yield 44.1 g., 84%).

Anal. Calcd. for $C_9H_{11}NO_2S$: C, 55.1; H, 5.6; S, 16.3. Found: C, 54.9; H, 5.6; S, 16.2; S (as –SH), nil; λ_{co}, 6.03 μ.

(b) **2-Hydroxyethyl *p*-methoxythiolcarbanilate** (I, R = C_6H_4OMe) was prepared similarly by the reaction of *p*-methoxyphenyl isocyanate (10 g., 0.067 mole) with 2-mercaptoethanol (5.5 g., 0.07 mole) in 50 ml. of benzene containing one drop of diethylcyclohexylamine at 40°. The product after recrystallization from benzene had m.p. 108–110°.

Anal. Calcd. for $C_{10}H_{13}NSO_3$: C, 52.9; H, 5.7; S, 14.2. Found: C, 53.0; H, 5.7; S, 14.2; S (as –SH), nil; λ_{co}, 6.03 μ.

(c) **2-Hydroxyethyl 1-naphthylthiolcarbamate** (I, R = $C_{10}H_7$), prepared from 1-naphthyl isocyanate (10 g., 0.063 mole) and 2-mercaptoethanol (5 g., 0.064 mole) in 35 ml. of benzene containing one drop of diethylcyclohexylamine catalyst, had m.p. 105–107° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{13}H_{13}NSO_2$: C, 63.1; H, 5.2; S, 12.9. Found: C, 63.3; H, 5.2; S, 13.0; S (as –SH), nil; λ_{co}, 6.07 μ.

Preparation of Bis-urethans of 2-Mercaptoethanol. (a) **2-(*p*-Methoxycarbaniloylthio)-ethyl *p*-methoxycarbanilate** (V, R = C_6H_4OMe) was prepared by the reaction of 2-hydroxyethyl *p*-methoxythiolcarbanilate (2 g., 0.0088 mole) with *p*-methoxyphenyl isocyanate (3.05 g., 0.0205 mole) in 30 ml. of benzene containing two drops of diethylcyclohexylamine. The solid which separated after 4 hours of refluxing

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[7] C. B. Ryland and M. W. Tamele, *Ind. Eng. Chem., Anal. Ed.*, **8**, 16 (1936).

[8] λ_{co}, Wave length of infrared carbonyl absorption maximum.

had m.p. 178–179° after recrystallization from ethyl acetate. It was identical with the product of reaction of *p*-methoxyphenyl isocyanate with 2-mercaptoethyl *p*-methoxycarbanilate in the same proportions.

Anal. Calcd. for $C_{18}H_{20}N_2SO_5$: C, 57.4; H, 5.3; S, 8.5. Found: C, 57.3; H, 5.3; S, 8.5; λ_{co}, 6.10 and 5.97 μ.

(b) **2-(1-Naphthylcarbamoylthio)-ethyl 1-Naphthylcarbamate** (V, R = $C_{10}H_7$).—A solution of 2-hydroxyethyl 1-naphthylthiolcarbamate (2.0 g., 0.009 mole), 1-naphthyl isocyanate (0.5 g., 0.01 mole) and one drop of diethylcyclohexylamine in 30 ml. of benzene was refluxed for two hours. The product which separated on addition of ligroin had m.p. 177–178° after recrystallization from ethyl acetate. It was identical with the reaction product of 1-naphthyl isocyanate and 2-mercaptoethyl 1-naphthylcarbamate.

Anal. Calcd. for $C_{24}H_{20}N_2SO_3$: C, 69.1; H, 4.8; S, 7.7. Found: C, 69.0; H, 4.8; S, 7.5; λ_{co}, 6.02 and 5.87 μ.

(c) **2-Carbaniloylthioethyl carbanilate** (V, R = C_6H_5) was prepared by reaction of 2-mercaptoethyl carbanilate or 2-hydroxyethyl thiolcarbanilate with phenyl isocyanate. It had m.p. 148–150°; (lit.[4] gives 146°), λ_{co} 6.00 and 5.85 μ.

Preparation of Disulfides. (a) **Dithiodiethylene Carbanilate.**—2-Mercaptoethyl carbanilate (10 g., 0.051 mole) in 50 ml. of ethanol was stirred during the addition of a solution of ferric chloride (10 g. anhydrous, 0.062 mole) in 50 ml. of ethanol. The copious precipitate which separated was filtered off, washed with ethanol and recrystallized from ethyl acetate to give dithiodiethylene carbanilate (III, R = C_6H_5), m.p. 142–143°.

Anal. Calcd. for $C_{18}H_{20}N_2O_4S_2$: C, 55.0; H, 5.0. Found: C, 55.1; H, 5.1; λ_{co}, 5.83 μ.

The same compound was obtained by oxidation of 2-mercaptoethanol and reaction of the product with phenyl isocyanate.

(b) **Dithiodiethylene *p*-methoxycarbanilate** (III, R = C_6H_4OMe) was prepared by a similar oxidation of 2-mercaptoethyl *p*-methoxycarbanilate. It had m.p. 147–148° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{20}H_{24}N_2O_6S_2$: S, 14.1. Found: S, 14.1; λ_{co}, 5.87 μ.

(c) **Dithiodiethylene 1-naphthylcarbamate** (III, R = $C_{10}H_7$) had m.p. 147–148°. It was prepared by a similar oxidation of 2-mercaptoethyl 1-naphthylcarbamate.

Anal. Calcd. for $C_{26}H_{24}N_2O_4S_2$: S, 12.9. Found: S, 12.9; λ_{co}, 5.87 μ.

Action of Alkali on 2-Mercaptoethyl Carbamates. (a) **Aqueous Sodium Hydroxide.**—2-Mercaptoethyl carbanilate (3.94 g., 0.02 mole) was melted on a steam-bath and treated with 10% sodium hydroxide solution (8 ml., 0.02 mole). The clear solution, which formed initially, quickly clouded and began to deposit solid with a slight evolution of heat (40–50°). After 30 minutes the solid was filtered off, washed with water and recrystallized a number of times from ethyl acetate to give the polysulfide (VI, R = C_6H_5, n = 3–4), m.p. 112–114°.

Anal. Calcd. for $C_{15}H_{23}NO_2S_4$: C, 47.7; H, 6.1; N, 3.7; S, 33.9; mol. wt., 377. Found: C, 48.8; H, 5.7; N, 3.4; S, 32.9; mol. wt., 353; λ_{co}, 5.87 μ.

Aniline was obtained from the aqueous filtrates from the initial preparation, and identified by conversion to carbanilide, m.p. 238–240°.

(b) **Methanolic Potassium Hydroxide.**—2-Mercaptoethyl carbanilate (10 g., 0.05 mole) was dissolved in 50 ml. of anhydrous methanol and treated with 10% methanolic potassium hydroxide (56 ml., 0.15 mole). A slight increase in temperature occurred (30–40°) and a solid began to precipitate in two minutes. The mixture of potassium carbonate and product was filtered off, washed with methanol (dried yield 7.0 g.), dilute hydrochloric acid (vigorous effervescence) and water. Recrystallization (once) from ethyl acetate gave the polysulfide (IV, R = C_6H_5, n = 4), m.p. 112–114° (yield 1.2 g.).

Anal. Calcd. for $C_{15}H_{23}NO_2S_4$: C, 47.7; H, 6.1; S. 33.9; N, 3.7. Found: C, 47.8; H, 5.6; S, 33.5; N, 3.7.

Similarly, 2-mercaptoethyl *p*-methoxycarbanilate (10 g.) afforded a polysulfide (VI, R = C_6H_4OMe, n = 3–4), m.p. 145–147° (1.2 g.) on reaction with methanolic potassium hydroxide.

Anal. Calcd. for $C_{14}H_{21}NO_3S_3$: C, 48.8; H, 6.1; S, 27.6. Found: C, 48.6; H, 5.7; S, 29.8.

(c) **Sodium *t*-Butoxide.**—2-Mercaptoethyl carbanilate (10 g., 0.05 mole) in tetrahydrofuran (100 ml.) was treated at room temperature with a solution of sodium *t*-butoxide in tetrahydrofuran (20 ml., 0.05 mole). The solid which precipitated was filtered off, washed with water and recrystallized from ethyl acetate to give the polysulfide (VI, R = C_6H_5, n = 7–8), m.p. 118–120° (3.02 g.).

Anal. Calcd. for $C_{23}H_{39}NO_2S_8$: C, 44.7; H, 6.3; N, 2.3; S, 41.4. Found: C, 44.5; H, 6.1; N, 2.1; S, 39.6.

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WILMINGTON, DEL.

[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY OF THE ORTHO RESEARCH FOUNDATION]

Synthetic Oxytocics. II.[1] Condensation of Indolylmagnesium Bromide with Heterocyclic Aldehydes. Synthesis of 2,3-Benzo-7,8-(2',3'-indolo)-tetrahydroquinolizine

BY HENRY BADER AND WILLIAM OROSHNIK

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Indolylmagnesium bromide, although it fails to react normally with aliphatic and aromatic aldehydes, was found to give 3-indolylcarbinols with 2- and 4-pyridine- and 3-isoquinoline-aldehydes. 3-Indolyl-3'-isoquinolylcarbinol was converted by the route described in Part I[1] to the pentacyclic 2,3-benzo-7,8-(2',3'-indolo)-tetrahydroquinolizine and its methochloride.

The finding, in Part I of this series, that 3-indolealdehyde condenses normally with 2-pyridyllithium made possible a very convenient synthesis of 2-skatylpiperidine (II) through the pyridylcarbinol I (Chart I). In endeavoring to extend the scope of this synthetic route, we also investigated the alternative possibility of obtaining carbinols, such as I, through the condensation of indolylmagnesium bromide with the readily available pyridine-,[2] quinoline-,[3] or isoquinoline[4]-aldehydes.

Actually, the reported experiences with indole Grignard reagents and various aliphatic and

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[1] Part I, H. Bader and W. Oroshnik, THIS JOURNAL, **79**, 5686 (1957).

[2] W. Mathes, W. Sauermilch and T. Klein, *Chem. Ber.*, **84**, 452 (1951); V. M. Micovic and M. Lj. Mihailovic, *Rec. trav. chim.*, **71**, 970 (1952); J. P. Wibaut and R. Huls, *ibid.*, **71**, 1021 (1952); V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1956).

[3] A. H. Cook, I. M. Heilbron and L. Steger, *J. Chem. Soc.*, 413 (1943).

[4] B. R. Brown, D. H. Hammick and B. H. Thewlis, *ibid.*, 1145 (1951); C. E. Teague and A. Roe, THIS JOURNAL, **73**, 688 (1951).