appropriate times, placed in screw-capped vials, quickly cooled in ice water, and then stored in a freezer (−15°). Analysis of the samples was carried out at 230 nm for hydantoic acids without aryl substitution, and at 242.5 nm for the acids with aryl substitution. The extinction coefficients of the hydantoic acids are about one-third those of the respective hydantoin. The rate constants were obtained by plotting log $(A_\infty - A_t)$ *vs.* time, where A_∞ and A_t are the absorbance readings at infinity and at time t, respectively. Reactions carried out at 50.0 ± 0.1° in the methanol–water mixture were done in ampoules to prevent evaporation problems. The reverse of the ring-closure reactions was studied under identical conditions, but no visible reactions were noted, suggesting that the reactions were for all practical purposes irreversible under the conditions employed. Similarly, the spectrum of the reaction product for the ring-closure reactions was identical with that of an equimolar solution of the respective hydantoin.

pK_a Measurements.—pK_a's were measured in a water-jacketed cell maintained at 25° under nitrogen. The apparatus and method of determination, with slight modification, was that described by Albert and Sargent[38] for carboxylic acids with low water solubility. The hydantoic acids (~0.001 mol) were dissolved in 100 ml of standard sodium hydroxide solution (0.01909 *M*, μ 1.0 with NaCl) and then back-titrated with standard hydrochloric acid solution (0.1090 *M*, μ 1.0 with NaCl). The first end point gave the concentration of the dissolved acid and the remaining points were used to calculate the pK_a, correcting for the concentration of hydrogen ions. The reactions studied were carried out at 50°, but the pK_a's were determined at 25°. King[39] has determined the thermodynamic pK_a's of some hydantoic acids at 25 and 50°, and the average variation in the pK_a's in going from 25 to 50° was 0.02. Estimation of the pK_a' values at 50° was accomplished by the addition of 0.02 to each pK_a value determined at 25°.

Acknowledgment.—This work was supported by the Institute of Pharmaceutical Chemistry. The authors also wish to thank Drs. I. H. Pitman, R. L. Schowen, and T. C. Bruice for helpful discussions.

(38) A. Albert and E. P. Sargent, "Ionization Constants of Acids and Bases," Methuen, London, 1962.

(39) E. J. King, *J. Amer. Chem. Soc.*, **78**, 6020 (1956).

3-Substituted Propionaldehyde Derivatives. A Study of the Chemistry of 2-Hydroxymethylglyceraldehyde Acetonide[1]

GEORGE JUST* AND PHILLIP ROSSY[2]

Department of Chemistry, McGill University, Montreal 101, Quebec, Canada

Received September 21, 1972

The reaction of glyceraldehyde acetonide with formaldehyde gave the 4-hydroxy-1,3-dioxolane II. Distillation of II gave hydroxymethylglyceraldehyde acetonide VI, characterized as its dimethylhydrazone V, dimethylacetal VII, and *N*-methyloxazolidine derivative X. The latter compound proved to be stable to acetylation and mesylation, and the protecting group could be removed under very mild acidic conditions, allowing the synthesis of aldehydomesylate IX and aldehydothioacetate XIIa.

The replacement of the alcohol function of a β-hydroxyaldehyde is a difficult undertaking because of the ease of polymerization of such compounds. We would like to report on the synthesis and some reactions of 2-hydroxymethylglyceraldehyde acetonide, and its transformation to the 3 mesylate and 3 thioacetate in both a protected and unprotected form. Some of these compounds were required in large quantities in connection with a cepham synthesis.

Glyceraldehyde acetonide I[3] was treated with formaldehyde in aqueous methanolic potassium carbonate. Crystallization of the reaction mixture gave II in 70% yield. Its structure was determined from its reactions and from analytical and spectroscopic data. Also, 4-hydroxy-1,3-dioxanes are known to arise from the reaction of aldehydes with aldols.[4]

The acetate IIa was prepared, but was difficult to obtain in crystalline form. This was due to the fact that two isomers were present in the reaction mixture, as evidenced by the nmr spectrum, which showed two singlets for the anomeric proton at 5.65 and 5.85 ppm in a ratio of 3:1. A method was devised to achieve selective hydrolysis of the acetonide function of the acetate mixture IIa, and the diol mixture IIIa was obtained in very good yield. The method consisted of treatment of the acetonide IIa with 90% aqueous trifluoroacetic acid for 2 min. The resulting diol acetate IIIa was converted to an oily mesylate IVa, but no further work was done on it, since it could not be obtained crystalline.

However, the mixture of epimeric *p*-nitrobenzoates IIb was easily prepared in crystalline form, even though two isomers were obtained (two singlets for the anomeric proton at 6.3 and 6.5 ppm, ratio 3:1). It is evident from the nmr spectrum that the isomer in which the *p*-nitrobenzoate is equatorial is favored.[5] Compound IIb could be converted to a crystalline mixture of epimeric diols IIIb and a crystalline mixture of epimeric mesylates IVb. Attempts to displace the mesylate with potassium thioacetate or with sodium hydrogen sulfide, and to extrude formaldehyde in order to regenerate a hydroxyaldehyde, failed.

While carrying out these reactions, we noticed that high-temperature distillation of compound II gave the aldehyde VI, which we had wanted in the first place. The ir spectrum indicated the presence of an aldehyde (1730 cm^{-1}) and a hydroxyl group (3400 cm^{-1}). The nmr spectrum was consistent with the proposed structure. Upon standing at room temperature for a few hours, the hydroxyaldehyde became very viscous and the carbonyl absorption in the ir decreased considerably. Aldols are known[4] to polymerize or dimerize on standing. It was thus necessary to protect the alde-

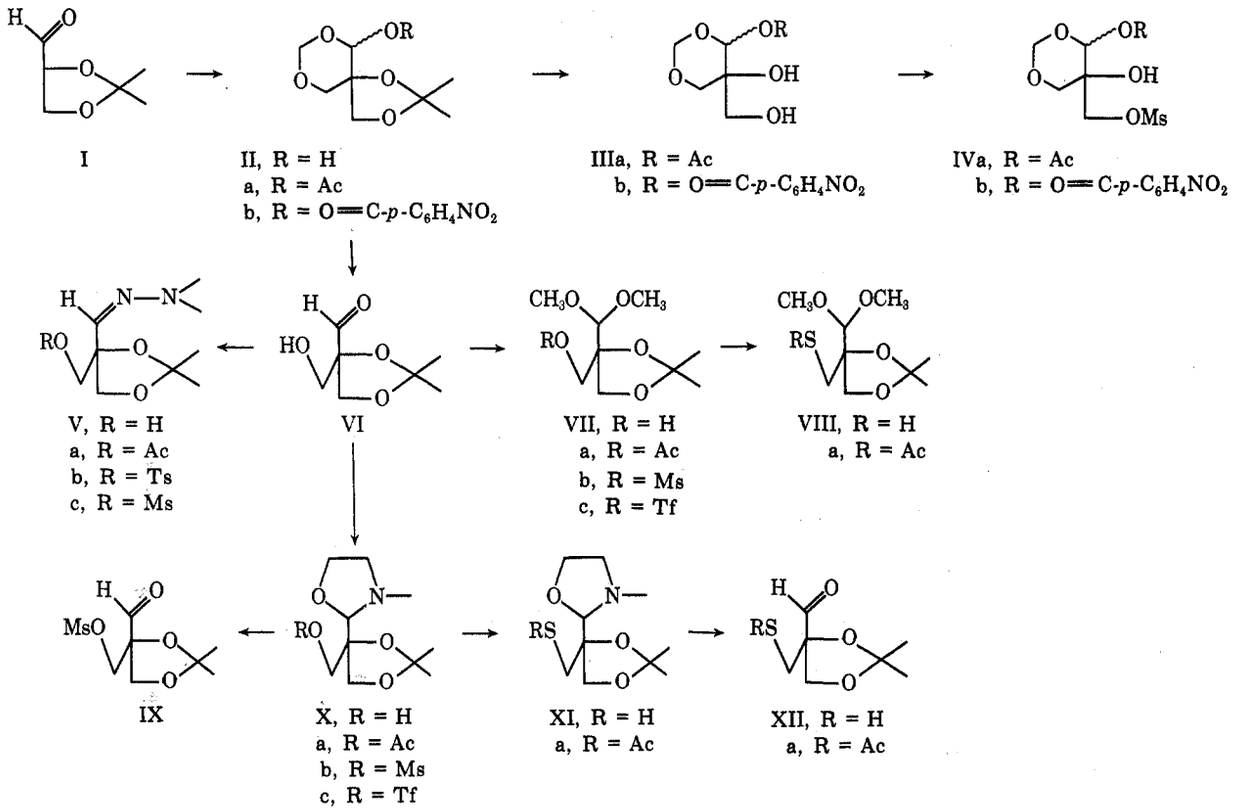
(1) We wish to thank the National Research Council of Canada and Bristol Laboratories, Syracuse, N. Y., for financial support.

(2) Abstracted from part of the Ph.D. thesis of Phillip Rossy.

(3) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 463 (1939).

(4) C. A. Friedmann and J. Gladych, *J. Chem. Soc. C*, 3687 (1954).

(5) Axial protons appear at higher field than the corresponding equatorial protons: R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, pp 19–20.



hyde function, before attempting to convert the hydroxy function to a good leaving group. The first derivative to be considered was a *N*,*N*-dimethylhydrazone. They are known to be hydrolyzed[6] rapidly by treatment with 95% ethanol, after quaternization with methyl iodide. The aldol VI was treated with dimethylhydrazine in ethanol and a 75% yield of V was obtained. It was easily converted to its acetate Va, tosylate Vb, and mesylate Vc. However, attempted displacement of the mesylate group with potassium thioacetate or sodium hydrogen sulfide gave intractable materials, presumably because of intramolecular cyclization. It was shown by an nmr study that the tosylate Vb decomposed on standing in methanol for a few hours. No attempts were made to isolate the products of the deterioration of this compound.

Next, the aldehyde was protected as its dimethyl acetal VII, which was obtained using carefully defined conditions in 60–65% yield. Compound VII was converted easily to its acetate VIIa, mesylate VIIb, and trifluoromethanesulfonate[7] VIIc. Displacement of the mesylate was accomplished by refluxing for several days with potassium thioacetate or sodium hydrogen sulfide in acetone or methanol. Displacement of the triflate group in VIIc could be carried out in a few hours, giving the pure thioacetate VIIIa. The thiol VIII could be obtained directly from the triflate VIIc by reaction with sodium hydrogen sulfide or by hydrolysis of the thioacetate VIIIa using sodium methoxide in methanol.

Further work on this approach was discontinued when it was realized that attempts to selectively hydrolyze the acetal function of VIII or VIIIa using the usual hydrolytic methods (80% acetic acid, 10% hydrochloric acid, 2% sulfuric acid, and 10% aqueous oxalic acid at room temperature) led to hydrolysis of both the acetonide and acetal groups. No selectivity was evident, and all the above-mentioned conditions led to polymerization products.

Transketalization is a very effective method in removal of ketals. However, only the starting material was recovered when VIIa was treated at room temperature with acetone and a trace of *p*-toluenesulfonic acid for prolonged periods of time. The reaction was followed by nmr using acetone-d_6 as solvent. Exchange of the acetonide function by a deuterioacetonide group was observed, but there was no change in the methoxy absorption.

Sjöberg[8] brought to our attention the possibility of using oxazolidines[9] as protecting groups for aldehydes. Treatment of the hydroxyaldehyde VI with *N*-methylethanolamine in diethyl ether afforded the oxazolidine X. Examination of the product using vpc analysis showed the existence of one major component and an impurity of approximately 10%. Distillation did not remove the impurity. Attempted purification on a silica column led to hydrolysis of the protecting group, but filtration through alumina, using benzene as eluent, afforded pure X in an overall yield of 55%. It could be converted to acetate Xa in quantitative yield. A study was made to determine the ease of hydrolysis of the oxazolidine. The hydrolysis of Xa was followed by nmr spectroscopy in 50% deuterium oxide and acetic acid-d_4. The reaction was complete in 15 min, as evidenced by the shift of the *N*-methyl absorption from 2.5 to 2.9 ppm. Xa could also be hydrolyzed in a two-

(6) M. Avaro, J. Levisalles, and H. Rudler, *Chem. Commun.*, 445 (1969).
(7) T. M. Su, W. Sliwinki, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 5386 (1969).
(8) We wish to thank Dr. K. Sjöberg for helpful discussions pertaining to the oxazolidine chemistry.
(9) W. Watanabe and L. Conlon, *J. Amer. Chem. Soc.*, **79**, 2825 (1957).

phase system. The oxazolidine was dissolved in chloroform-*d* and to this solution was added a 50% solution of acetic acid-d_4 in D_2O. Following the disappearance of the *N*-methyl absorption in the nmr (owing to the solubility of *N*-methylethanolamine in the upper heavy-water phase), it was shown that the hydrolysis was complete in 1 hr at room temperature.

Alcohol X could be converted to its crystalline mesylate Xb in 80% yield, using methanesulfonyl chloride and triethylamine. Hydrolysis of the oxazolidine mesylate Xb gave the aldehyde mesylate IX.

Attempts to carry out a nucleophilic displacement on the mesylate IX with thiolate anions gave addition products onto the aldehyde, rather than displacement of the mesylate function. In order to increase the reactivity of the leaving group an attempt was made to prepare the triflate of alcohol X. When the reaction was carried out using trifluoromethanesulfonic anhydride in pyridine, a sulfonamide was obtained which was not further characterized. When an excess of triethylamine was used, triflate Xc could be obtained. It was, however, contaminated by sulfonamide, and since triflates are quite unstable no attempt was made to purify it.

Since all attempts to form a pure trifluoromethanesulfonate in the presence of an oxazolidine ring failed, work was continued using the mesylate Xb. It was converted to the thioacetate XIa by displacement using potassium thioacetate in refluxing acetone for 2–3 days. The aldehyde thioacetate XIIa was easily prepared by aqueous acetic acid hydrolysis.

An effort to hydrolyze XIIa to the thiol aldehyde XII using ammonia in methanol or a trace of sodium methoxide in methanol gave intractable mixtures from which no products could be isolated.

From this result, and the fact that aldehyde mesylate IX reacted with thiolate anions at the aldehyde function, it would appear that the thiol aldehyde XII cannot be isolated using normal laboratory procedures.

However, other compounds of type XII, where R is alkyl or vinyl, could be prepared. They will form the subject of another publication.

Experimental Section

Melting points were determined on a Gallenkamp block and are uncorrected. Mass spectra were obtained on an AE1-MS-902 mass spectrometer at 70 eV using a direct-insertion probe. Nmr spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane as the internal standard. The multiplets and quartets in the nmr spectral data were recorded as the center of the peaks. Ir spectra were obtained on a Unicam SP1000 and a Perkin-Elmer 257 infrared spectrophotometer. Ultraviolet spectra were determined with a Unicam SP-800 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter.

Thin layer chromatography was performed on silica gel coated plates (Eastman). Woelm aluminum oxide (neutral) and silica gel were used for column chromatography. Microanalyses were carried out by A. Bernhardt, Mikroanalytisches Laboratorium, Elbach uber Engelskirchen, C. Daessle, Montreal, and F. Pascher, Bonn, West Germany.

Formaldehyde Adduct II.—Freshly distilled glyceraldehyde acetonide (18 g) was added to a stirred solution of 18 g (2 equiv) of anhydrous potassium carbonate, 50 ml of a 40% aqueous formaldehyde solution, 100 ml of distilled water, and 200 ml of methanol. The clear solution was stirred at room temperature overnight. The solution was concentrated *in vacuo* (bath temperature <40°). The crystalline mass (product and potassium carbonate) was extracted three times with 60-ml portions of methylene chloride. The solvent was dried with sodium sulfate, filtered, and evaporated to a clear oil which crystallized spontaneously when the last traces of solvent were removed under high vacuum. The colorless, crystalline compound was recrystallized from ether–methylene chloride mixtures. An analytical sample was prepared by sublimation [90° (0.2 mm)]: yield 20.8 g (80%); mp 89.5–91°; ir (KBr) 3400 (OH str), 1380, 1220, 1160, 1090, 1080, 1050, 1000 cm^{-1}; nmr ($CDCl_3$) δ 1.5 (s, 6), 3.9 [AB q, 2, J = 10 Hz, $CH_2OC(CH_3)_2$], 4.2 (AB q, 2, J = 10 Hz), 5.0 (AB q, 2, J = 7 Hz, $COCH_2O$), 5.1 (s, 1), 4.0–6.0 ppm (broad, 1, OH); mass spectrum (70 eV) *m/e* 190 (m^+).

Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.57; H, 7.52.

Acetate IIa.—The hydroxydioxane II was acetylated using pyridine and acetic anhydride: yield 89%; mp 30–31.5° (ether–carbon tetrachloride); ir (NaCl film) 1750 (C=O str), 1380, 1170–1280 (C–O str), 1120, 1080, 1010, 930 cm^{-1}; nmr (CCl_4) δ 1.3 (s, 6), 2.1 (s, 3, CH_3CO–), 3.7 (AB q, 2, J = 10 Hz), 3.9 (AB q, 2, J = 10 Hz), 4.8 (AB q, 2, J = 7 Hz), 5.65, 5.85 (double singlets, 1, CHOAc, two isomers); mass spectrum (70 eV) *m/e* 232 (M^+), 173 ($M^+ - OCOCH_3$).

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.51; H, 6.98.

Hydrolysis of Acetonide Acetate IIa to Diol IIIa.—The acetate IIa (2.3 g, 10 mmol) was dissolved in 250 ml of 80% aqueous acetic acid and heated at 60° for 15 hr. The acetic acid was evaporated under high vacuum to half of the original volume, diluted with 125 ml of water, and extracted with three 100-ml portions of methylene chloride. The solvent was dried over sodium sulfate, filtered, and evaporated to yield 1.5 g of a light yellow oil. The oil crystallized only with difficulty (methanol–ether): yield 79%; mp 109–110.5°; ir (NaCl film) 3300–3500 (OH str), 1740 (C=O str), 1390, 1260, 1050 cm^{-1}; nmr (pyridine-d_5) δ 2.0 (s, 3), 4.2 (AB q, 2, J = 10 Hz), 4.3 (s, 2, CH_2OH), 4.8 (AB q, 2, J = 7 Hz), 5.6 ppm (double s, CHOAc, two isomers).

Anal. Calcd for $C_7H_{12}O_6$: C, 43.75; H, 6.29. Found: C, 43.97; H, 6.09.

Another method was used to hydrolyze the acetonide: 100 mg of the acetate IIa was dissolved in 1 ml of 90% aqueous trifluoroacetic acid and stirred at room temperature for 2 min. Flash evaporation under high vacuum and evaporation several times with methanol and toluene removed the last traces of acid. The resulting oil crystallized from a methanol and ether mixture, yield 66 mg (80%).

Preparation of *p*-Nitrobenzoate IIb.—The alcohol II (4.75 g) was dissolved in 25 ml of dry pyridine, and 5.2 g of recrystallized *p*-nitrobenzoyl chloride (from CCl_4) was added at once. The reaction mixture was stirred at 0° for 2 hr and at 25° for 12 hr. The precipitated mass was stored at −20° for 24 hr. Saturated sodium bicarbonate solution (30 ml) was added while the mixture was being ice cooled. Stirring was continued for 15 min and then the mixture was poured into 300 ml of ice-cold water. Rapid stirring was continued for 1 hr and then the precipitate was filtered, air dried, and recrystallized from chloroform: yield 7.0 g (82.5%); mp 228–229.5°; ir (KBr) 1740, 1610, 1540, 1360, 1270, 1100, 1060 cm^{-1}; nmr ($CDCl_3$) δ 1.6 (d, 6), 3.85 (AB q, 2, J = 10 Hz), 4.1 (s, 2), 5.1 (AB q, 2, J = 7 Hz, OCH_2O–), 6.3, 6.55 (double s, 1), 8.5 ppm (s, 4); mass spectrum (70 eV) *m/e* 339 (M^+). It was apparent from the nmr spectrum that the two epimers were in a ratio of 3:1.

Anal. Calcd for $C_{15}H_{17}NO_8$: C, 53.10; H, 5.05; N, 4.13. Found: C, 52.92; H, 4.01; N, 4.25.

Hydrolysis of Acetonide IIb to Diol IIIb.—The procedure for the hydrolysis of acetonide IIa using trifluoroacetic acid was used. From 300 mg of IIb and 2 ml of 90% aqueous trifluoroacetic acid, 227 mg (84%) of IIIb was obtained. It was crystallized from methanol: mp 122–124° (softens 115°); ir (NaCl film) 3400–3300, 1740, 1610, 1530, 1350, 1270, 1170, 1100, 1090, 1050, 880, 720 cm^{-1}; nmr (DMSO-d_6) δ 3.8 (s, 2, CH_2OH), 3.8–4.0 (broad singlet, 2, OH), 4.0 (AB q, 2, J = 10 Hz), 5.0 (AB q, 2, J = 7 Hz, OCH_2O), 6.1, 6.4 ppm (double singlet, 1, epimeric hydrogen α to *p*-NBz), 8.7 ppm (s, 4).

Anal. Calcd for $C_{12}H_{13}NO_8$: C, 43.75; H, 6.29; N, 4.68. Found: C, 43.97; H, 6.09; N, 4.79.

Preparation of the Mesylate IVb.—Mesylate IVb was prepared by treating IIIb with mesyl chloride in pyridine at 0°: yield from 2.99 g, 3.1 g (80%); mp 146–148° (methanol); ir (KBr) 3500, 1740, 1610, 1540, 1340 (SO_2 str), 1260, 1250, 1180, 1170, 830,

720 cm^{-1}; nmr (acetone-d_6) δ 3.13 (s, 3, OMs), 4.0 (AB q, 2, J = 10 Hz, OCH_2C), 4.5 (s, 2, CH_2OMs), 5.0 (AB q, 2, J = 7 Hz), 4.8–5.2 (broad, 1, OH), 6.2 ppm (s, 1, CHOBzN-p), 8.4 ppm (s, 4); mass spectrum (70 eV) m/e 281 ($M^+ - HOSO_2CH_3$).

Preparation of Hydroxyaldehyde VI.—The formaldehyde adduct II (16 g) was placed in a 35-ml round-bottom flask, and immersed in an oil bath at 140°. The crystalline material melted and a strong odor of formaldehyde was detected. Partial vacuum was applied, while the temperature of the bath was raised to 160°. An odorless, colorless oil distilled at 101–104° (0.7 mm), yield 10.4 g (77%). Runs of 20–25 g are recommended, as the product is unstable to heat and a rapid distillation is necessary, otherwise the yield of polymerized materials increases. The nmr showed the following peaks: δ 1.7 (s, 6, acetonide), 4.0 (AB q, 2, J = 8 Hz, CH_2OH), 3.9 (s, 1, OH), 4.25 (AB q, J = 10 Hz), and 10.4 ppm (s, 1, aldehyde). The ir (NaCl film) had a strong absorption at 3300–3500 cm^{-1} (hydroxyl) and a strong aldehyde absorption at 1735 cm^{-1}.

Upon standing for a few hours, the hydroxyaldehyde polymerized; thus reactions involving this intermediate must be carried out immediately.

N,N-Dimethylhydrazone V.—Into a 50-ml, two-necked flask equipped with a reflux condenser, drying tube, and rubber septum was added 2–3 g of barium oxide and a solution of 2.1 ml (1.5 equiv) of 1,1-dimethylhydrazine (distilled twice over barium oxide) in 20 ml of absolute ethanol. To the cooled solution was added dropwise 2.9 g of aldehyde V dissolved in 10 ml of absolute ethanol. The addition was made over a period of 30 min. After the initial exothermic reaction had subsided the reaction mixture was refluxed for 1 hr. The cooled solution was filtered and evaporated to yield a light yellow oil. Yield after distillation was 2.7 g (75%); bp 98–99° (0.7 mm); ir (NaCl film) 3600–3300 (OH str), 2830, 2820, 2800 [$N(CH_3)_2$], 1600, 1480, 1460, 1370, 1260, 1220, 1070, 1050, 1030 cm^{-1}; nmr ($CDCl_3$) δ 1.5 (s, 6), 2.9 [s, 6, $N(CH_3)_2$], 3.5 (s, 1, OH), 3.7 (s, 2, CH_2OH), 4.1 ppm [s, 2, $CH_2OC(CH_3)_2$], 6.6 ppm (s, 1, HC=N); mass spectrum (70 eV) m/e 202 (M^+).

Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.44; H, 8.97; N, 13.85. Found: C, 53.63; H, 8.79; N, 13.34.

Preparation of the Acetate Va.—The acetate was prepared in the usual manner using acetic anhydride and pyridine. The yield of crude product was quantitative: ir (NaCl film) 2830, 2816, 2790 [$N(CH_3)_2$], 1740 (C=O str), 1600, 1460, 1450, 1380, 1370, 1250, 1050 cm^{-1}; nmr ($CDCl_3$) δ 1.45 (s, 6), 2.1 (s, 3), 2.8 (s, 6), 4.15 (AB q, 2, J = 9 Hz, CH_2OAc), 4.3 (s, 2), 6.6 ppm (s, 1).

Anal. Calcd for $C_{11}H_{20}N_2O_4$: C, 54.09; H, 8.14; N, 11.47. Found: C, 53.98; H, 8.01; N, 11.34.

Preparation of Dimethyl Acetal VII.—To 100 ml of absolute methanol (distilled over magnesium turnings) and 10 mg of p-toluenesulfonic acid was added 10 g of molecular sieves 3A and 1.6 g (10 mmol) of the aldehyde. The mixture was stirred (with exclusion of moisture) for 12–15 hr at room temperature. After neutralization of the acid with ion exchange resin [Rexyn 203 (OH)], filtration, evaporation and distillation, pure acetal was obtained in 60% yield (1.24 g): bp 100–102° (0.5 mm); ir (NaCl film) 3600–3300 (OH str), 1470, 1410, 1390, 1270, 1230, 1120, 1100, 1080 cm^{-1}; nmr ($CDCl_3$) δ 1.55 (s, 6), 3.4 (s, 1, OH), 3.65 [s, 6, $(OCH_3)_2$], 3.8 (s, 2, CH_2OH), 4.1 (AB q, 2, J = 6 Hz, CH_2OC), 4.5 [s, 1, $HC(OCH_3)_2$].

Anal. Calcd for $C_9H_{18}O_3$: C, 52.41; H, 8.80. Found: C, 52.31; H, 8.68.

Acetate VIIa.—The compound was prepared in a 95% yield from the alcohol, by means of pyridine and acetic anhydride. Evaporation of the reagents afforded analytically pure acetate: ir (NaCl film) 1745, 1460, 1390, 1380, 1250 (C–O str), 1120, 1090, 1060 cm^{-1}; nmr ($CDCl_3$) δ 1.7 (s, 6), 2.4 (s, 3), 3.85 (d, 6), 4.2 (AB q, 2, J = 8 Hz, CH_2OC), 4.5 (AB q, 2, J = 8 Hz, CH_2OAc), 4.55 ppm [s, 1, CH $(OCH_3)_2$].

Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12. Found: C, 53.30; H, 7.94.

Mesylate VIIb.—This compound was prepared by the usual method with methanesulfonyl chloride and pyridine at 0°. After ether extraction, 85% yield of light yellow foam was obtained after the usual work-up procedure: nmr ($CDCl_3$) δ 1.45 (s, 6), 3.1 (s, 3, OMs), 3.6 (s, 6), 4.0 (AB q, 2, J = 10 Hz, CH_2OC), 4.3 [s, 1, HC $(OCH_3)_2$], 4.35 ppm (AB q, 2, J = 9 Hz, CH_2OMs).

Anal. Calcd for $C_{10}H_{20}O_7S$: C, 42.25; H, 7.04; S, 11.26. Found: C, 42.01; H, 7.15; S, 11.12.

Triflate VIIc.—The alcohol V (200 mg, 1 mmol) was dissolved in 3 ml of absolutely dry pyridine and the solution was cooled to −5° and protected from moisture by the use of a calcium chloride drying tube. Freshly prepared trifluoromethanesulfonic anhydride (850 mg, 5 equiv) (prepared[6] by flame distillation of the acid over phosphorus pentoxide, bp 85°) was added slowly to the cooled mixture. A color change from colorless to green to red was observed. The red solution was stirred for 5 min and immediately evaporated to dryness on a rotatory evaporator connected to a high vacuum pump (bath temperature must not exceed 35°). The deep red oil was dissolved in methylene chloride and washed with three portions of ice-cold water. The solvent was dried and evaporated to afford an orange-red oil (yield 85.5%, 290 mg). Because of the instability of the product no attempts were made at its purification. The ir spectrum showed no hydroxyl absorption and a large absorption band at 1420 and 1390 cm^{-1} (SO_2 str); nmr ($CDCl_3$) δ 1.5 (s, 6), 3.6 (s, 6) 4.1 [AB q, 2, J = 10 Hz, $CH_2OC(CH_3)_2$], 4.45 [s, 1, $CHC(OCH_3)_2$], 4.65 ppm (AB q, 2, J = 1 Hz, CH_2OTf).

Protection of Aldol VI using N-Methylethanolamine.—Anhydrous sodium carbonate (5 g) was suspended in an ice-cold solution of 1 g (1.1 equiv) of N-methylethanolamine in 30 ml of dry ether; 1.95 g of freshly prepared aldol, dissolved in 10 ml of anhydrous ether, was added dropwise over a period of 30 min. The mixture was stirred for an additional 30 min at 0° and then for 1 hr at room temperature. The filtered solution was evaporated and distilled [105–108° (0.75 mm)]. Crude yield was 2.1 g (80%). Vpc analysis (0.125 in. × 6 ft column of 3% OV-25 on 80–100 mesh Chromosorb W at 150° using a Hewlett-Packard Model 5750 B gas chromatograph) showed one major component (90%) and one minor component (10%). Filtration on an alumina (activity I) column using benzene as eluent afforded pure material (3 g of alumina for 1 g crude product). After purification a yield of 1.8 g of X (overall 55%) was obtained: ir (NaCl film) 3600–3300 (OH str), 2810 (NCH_3), 1470, 1380, 1260, 1225, 1150, 1080, 1070, 1050 cm^{-1}; nmr ($CDCl_3$) δ 1.45 (s, 6), 2.55, 2.60 (d, 3, NCH_3), 2.7 (m, 1, part of AA'BB' system of NCH_2-CH_2O), 3.3 (m, 1, NCH_2CH_2O), 4.0 ppm (m, 8, part of AA'BB' system, NCHO, two AB systems for CH_2OH and CH_2OC–, and OH); mass spectrum (70 eV) m/e 217 (M^+).

Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.82; N, 6.45. Found: C, 55.16; H, 8.72; N, 6.25.

Acetate Xa.—The usual procedure was used to prepare the acetate in quantitative yield. The sample was analytically pure after evaporation of the reagents: ir (NaCl film) 2810 (NCH_3), 1745 (C=O str), 1460, 1380, 1270–1210 (C–O str), 1110, 1080, 1060 (cm^{-1}); nmr ($CDCl_3$) δ 1.5 (s, 6), 2.25 (s, 3, OAc), 2.55 (s, 3, NCH_3), 2.8 (m, 1), 3.3 (m, 1), 4.2 ppm (m, 7).

Anal. Calcd for $C_{12}H_{21}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.28; H, 7.39; N, 5.24.

Mesylate Oxazolidine Xb.—To a solution of 217 mg (1 mmol) of the alcohol in 10 ml of methylene chloride containing 220 μl (1.5 mmol) of triethylamine at −10 to 0° was added 84 μl (1.1 mmol) of methanesulfonyl chloride over a period of 30 min. Anhydrous reaction conditions were maintained. Stirring from an additional 15–30 min completed the reaction. The mixture was transferred to a separatory funnel with the aid of more methylene chloride. The mixture was washed with ice water. Drying of the organic phase followed by solvent removal gave an oil. The oil was crystallized from methylene chloride–ether: yield 242 mg (82%); mp 79.5–81°; tlc R_f 0.6 (ether, SiO_2); ir (CCl_4 solution) 2810 (N–CH_3 str), 1470, 1380 (OMs), 1220, 1180, 1080, 1010 cm^{-1}; nmr ($CDCl_3$) δ 1.5 (s, 6), 2.6 (s, 3, NCH_3), 2.7 (m, 1), 3.2 (s, 3, OMs), 3.3 (m, 1), 3.8–4.6 ppm (m, 7).

Anal. Calcd for $C_{11}H_{21}NO_6S$: C, 44.75; H, 7.12; N, 4.75; S, 10.85. Found: C, 44.63; H, 7.18; N, 4.66; S, 10.63.

Displacement of Mesylate Xb using Potassium Thioacetate.—To a solution of 295 mg (1 mmol) of the mesylate in 20 ml of dry acetone was suspended 171 mg (1.5 mmol) of recrystallized potassium thioacetate. The mixture was refluxed, under a nitrogen atmosphere, for 3 days. Filtration of the cooled solution and evaporation of the acetone gave a pale yellow oil. The oil was dissolved in methylene chloride and washed with ice water. Drying of the organic layer and evaporation afforded 264 mg (96% of theory) of a pale yellow semicrystalline oil (XIa). The sample was analytically pure: nmr ($CDCl_3$) δ 1.5 (double singlet, 6), 2.4 (s, 3, SAc), 2.55 (s, 3, NCH_3), 2.7 (m, 1), 3.2 (m, 1), 3.35 (s, 2, CH_2SAc), 4.0 [AB q, 2, J = 10 Hz, $CH_2OC(CH_3)_2$], 4.0 ppm (s, 1).

Anal. Calcd for $C_{12}H_{21}NO_4S$: C, 52.36; H, 7.64; N, 5.09; S, 11.64. Found: C, 52.11; H, 7.53; N, 4.95; S, 11.22.

Hydrolysis of Thioacetate Oxazolidine XIa to Thioacetate XIIa.—The compound (57 mg) was treated with 10 ml of a 1:1 mixture of acetic acid and water for 15–30 min at room temperature. The aqueous solution was extracted with three portions of methylene chloride and the combined extracts were dried and evaporated first on a rotatory evaporator (water aspirator) and then on a high vacuum line, to remove the last traces of acetic acid. In this way, 41 mg (91% yield) of analytically pure XIIa was obtained: nmr ($CDCl_3$) δ 1.45, 1.5 (double singlet, 6), 2.45 (s, 3, SAc), 3.3 (s, 2, CH_2SAc), 4.1 (AB q, 2, J = 10 Hz, CH_2OC), 10 ppm (s, 1, CHO).

Anal. Calcd for $C_9H_{14}O_4S$: C, 49.54; H, 6.42; S, 14.68. Found: C, 49.41; H, 6.34; S, 14.48.

Registry No.—I, 5736-03-8; II, 38615-71-3; IIa, 38615-72-4; IIb, 38615-73-5; IIIa, 38615-74-6; IIIb, 38615-75-7; IVb, 38615-76-8; V, 38615-77-9; Va, 38615-78-0; VI, 38615-79-1; VII, 38615-80-4; VIIa, 38615-81-5; VIIb, 38615-82-6; VIIc, 38615-83-7; X, 38615-84-8; Xa, 38615-85-9; Xb, 38615-86-0; XIa, 38615-87-1; XIIa, 38615-88-2; 1,1-dimethylhydrazine, 57-14-7; trifluoromethanesulfonic anhydride 358-23-6; *N*-methylethanolamine, 109-83-1.

Relative Reactivities of Nucleophilic Centers in Some Monopeptides

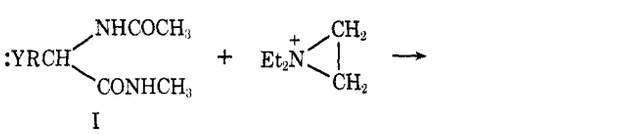
CHARLES C. PRICE,* HIROSHI AKIMOTO,[1] AND RICHARD HO[1]

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

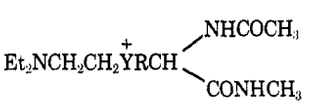
Received October 10, 1972

The "monopeptide" derivatives of a number of amino acids with nucleophilic centers have been prepared and their reactivity in water to diethylaziridinium ion, iodoacetic acid, and iodoacetamide determined. The reactivity of the imidazole ring of histidine, the mercaptan group of cysteine, the phenolate ion in tyrosine, and the sulfide group in methionine are all very nearly the same as that of these groups in model compounds. The sulfide group shows unexpectedly high reactivity when measured by iodoacetic acid or iodoacetamide.

As a sequel to studies of the effect of structure and conformation of nucleic acids on the reactivity of nucleophilic centers to alkylation,[2] we have now undertaken a similar investigation for proteins. As a prelude to study of the reactivity of nucleophilic centers in polypeptides, we have examined the nucleophilicity of some of the more significant nucleophilic centers in model "monopeptides," the *N*-acetylmethylamide derivatives of several amino acids. The alkylating agent used most generally has been the one utilized most extensively in the earlier nucleic acid studies, *N*,*N*-diethylaziridinium ion.



I

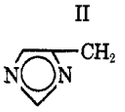


II

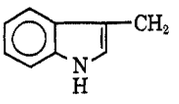
a, :YR = $HOC_6H_4CH_2$

b, :YR = $HSCH_2$

c, :YR = $CH_3SCH_2CH_2$



d, :YR =



e, :YR =

f, :YR = $HSCH_2CH_2$

Experimental Section

Materials.—*N*,*N*-Diethyl-2-chloroethylamine hydrochloride (Aldrich) was recrystallized from acetonitrile.

The monopeptides Ia, Ic, Id, and Ie were prepared from the corresponding amino acids essentially as described in the literature.[3a-c] Ib was prepared from the corresponding cystine derivative by zinc and acid reduction.[3d]

L-Homocysteine monopeptide (If) was prepared in much the same way as Ib. After addition of 1.56 g of thionyl chloride dropwise with stirring to a chilled suspension of 3.20 g of L-homocystine in 30 ml of absolute methanol, the reaction mixture was heated under reflux for 2 hr. After cooling, the solvent was removed *in vacuo* to give 4.4 g (theoretical yield) of colorless solid, L-homocystine dimethyl ester hydrochloride, which was used directly in the next step. This material and 5.35 g of triethylamine in 50 ml of $CHCl_3$ was chilled and 2.12 g of acetyl chloride was added dropwise with stirring. The reaction mixture was allowed to stand for 1 hr at room temperature and then washed and dried. After removal of the solvent, the crude product was recrystallized from ethyl acetate to give 4.3 g (94%) of *N*,*N*′-diacetyl-L-homocystine dimethyl ester as colorless needles, mp 105–106°, ir (Nujol) ν_{NH} 3800, ν_{CO} 1770, 1670 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_6N_2S_2$: C, 44.19; H, 6.36; N, 7.36; S, 16.85. Found: C, 44.07; H, 6.48; N, 7.39; S, 16.58.

After 3 days at room temperature, a solution of 3.8 g of this dimethyl ester in 40 ml of 40% aqueous methylamine was concentrated to dryness *in vacuo* to afford the desired compound in theoretical yield. The crude product was recrystallized from methanol to give 3.2 g (85%) of pure *N*,*N*′-diacetyl-L-homocystinmethylamide as colorless prisms, mp 188–189°, ir (Nujol) ν_{NH} 3350, ν_{CO} 1645, 1560, 1545 cm^{-1}.

Anal. Calcd for $C_{14}H_{26}O_4N_4S_2$: C, 44.42; H, 6.92; N, 14.80; S, 16.94. Found: C, 44.31; H, 6.86; N, 14.91; S, 16.76.

After 400 mg of zinc dust was added to 757 mg of this disulfide dissolved in 30 ml of 2 *N* aqueous acetic acid, 300 mg of concentrated sulfuric acid was dropped slowly into the stirred mixture over 15 min under nitrogen. The exothermic reaction raised the temperature to 35–40°. After this reaction mixture was warmed at 45–50° for 2 hr, it was concentrated to dryness *in vacuo*. The residue was extracted with three 25-ml portions of warm isopropyl ether, and the combined extract was evaporated *in vacuo* to give 670 mg (88%) of crude product. It was recrystallized from isopropyl ether under nitrogen atmosphere to yield 625 mg of *N*-acetyl-L-homocysteinmethylamide (If) as colorless prisms, mp 192–195°, ir (Nujol) ν_{NH} 3350, ν_{SH} 2600, ν_{CO} 1650 (sh), 1645, 1565, 1545 cm^{-1}.

Anal. Calcd for $C_7H_{14}O_2N_2S$: C, 44.19; H, 7.42; N, 14.72; S, 16.85. Found: C, 44.33; H, 7.71; N, 14.64; S, 16.81.

(1) Supported in part by NIH Grant No. NIGMS 19593.

(2) (a) C. C. Price, G. M. Gaucher, P. Koneru, R. Shibakawa, J. R. Sowa, and M. Yamaguchi, *Biochim. Biophys. Acta*, **166**, 327 (1968); (b) C. C. Price and M. T. L. Yip, in press; (c) Mei-Tak Lam Yip, "The Nitrogen Mustard Alkylation of Polynucleotides and Ribonucleic Acids," Ph.D. Dissertation, University of Pennsylvania, 1972.

(3) (a) H. Zahn, *Z. Phys. Chem.*, **344**, 75 (1966); (b) T. H. Applewhite and C. Niemann, *J. Amer. Chem. Soc.*, **81**, 2208 (1959); (c) H. T. Huang and C. Niemann, *ibid.*, **73**, 3223 (1951) (d) T. A. Martin, D. H. Causey, A. L. Sheffner, A. G. Wheeler, and J. R. Corrigan, *J. Med. Chem.*, **10**, 1172 (1967).