general method of Bockmühl, *et al.*[6] The reaction time was shortened by refluxing the bromoketone with two equivalents of amine in absolute alcohol. The alcohol was removed completely under reduced pressure, ether was added and the amine hydrobromide removed. The ether filtrate was acidified with hydrochloric acid and the oily product induced to crystallize. It was then recrystallized from alcohol and ether. The yields ranged from 67 to 80%.

Aminoalcohols.—The aminoethanols were synthesized from the corresponding aminoketone salts by catalytic hydrogenation with palladium-on-charcoal in water. Methanol was used as the solvent for reduction of the benzyloxyaminopropiophenones. By careful removal of the solvent many of the final products were obtained directly. However, in a few cases it was necessary to precipitate the aminoalcohol bases with ammonia and reconvert to stable salts in anhydrous media.

In order to avoid catalytic debenzylation the N-benzyl derivatives, 1-(4-methoxyphenyl)-2-benzylaminoethanol and 1-(4-methoxyphenyl)-2-benzylmethylaminoethanol, were prepared from appropriate aminoketone salts by reduction with aluminum isopropoxide.[4]

1-(4-Hydroxyphenyl)-2-isopropylaminoethanol[3] and its 4-methoxy analog were N-methylated by reductive alkylation with formaldehyde.[5]

The aminoethanols, obtained in yields of 50 to 95%, and the aminopropanols, obtained in yields of 75 to 85%, are described in Table II.

RENSSELAER, NEW YORK

[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES, BROWN UNIVERSITY]

Reactions of Aminoalcohol–Aldehyde Anhydro Compounds

BY EUGENE P. GOLDBERG[1] AND HAROLD R. NACE

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Reactions of three aminoalcohol–aldehyde anhydro products, 2-propyl-4-ethyloxazolidine (10% Schiff base), 2-benzylideneamino-1-butanol (100% Schiff base) and 2-(2-ethylhexylideneamino)-1-butanol (80% Schiff base), have been investigated. Despite their different structural compositions, all three compounds yield oxazolidine derivatives with nitrosyl chloride, α-naphthyl isocyanate and phenyl isothiocyanate. A shift of the Schiff base–oxazolidine equilibrium to the cyclic structure is thus indicated. Nitrosation of anhydro compounds with nitrosyl chloride in anhydrous ether–pyridine provides the most satisfactory synthesis of N-nitrosoöxazolidines.

Aldehydes and ketones react with 1,2-aminoalcohols to yield anhydro compounds which are frequently referred to as oxazolidines or Schiff bases although they are most often equilibrium mixtures of the two forms. Bergmann[2] demonstrated that a general relationship exists between the structures of the reactants and that of the anhydro product. Bergmann[2] and McCasland[3] suggested that chemical evidence was inconclusive for the determination of the anhydro product structure and additional evidence is presented here in support of this conclusion.

In reactions such as reduction or hydrolysis, either of the two structural forms (oxazolidine or Schiff base) gives the same product.[2] However, with reagents that react with secondary amines and not with Schiff bases, the anhydro product structure might be expected to influence the reaction course. Both Bergmann[2] and McCasland[3] obtained N-benzoyl oxazolidines from anhydro products which were predominantly in the Schiff base form. Heusser[4] reported the N-acetylation of a steroid oxazolidine and Henry and Dehn[5] obtained substituted ureas from the reaction of Schiff base types with isocyanates, but did not establish the structure of the products. These works suggest that Schiff bases may isomerize to oxazolidines in reacting. However, Bergmann[2] has recently attempted the anisoylation of a Schiff base type and obtained only the N,O-dianisoylated aminoalcohol.

In the work reported here, reactions of three anhydro products having different oxazolidine–Schiff base compositions were studied and additional evidence for an equilibrium is presented.

The first anhydro product studied was 2-propyl-4-ethyloxazolidine, previously prepared[6] and estimated to be 90% in the cyclic form. The second compound studied was 2-benzylideneamino-1-butanol. This viscous liquid was prepared by azeotroping water from a boiling benzene solution of 2-amino-1-butanol and benzaldehyde. The infrared spectrum showed a very strong C=N band at 6.11μ and a molar refraction exaltation of 1.5 units (above the calculated Schiff base value) was found. These data indicated that this material was almost entirely in the Schiff base form.

The third anhydro compound investigated was 2-(2-ethylhexylideneamino)-1-butanol. This material was prepared, as above, from 2-amino-1-butanol and 2-ethylhexanal, and was identical with the previously reported 2-(2-ethyl-2-hexenylideneamino)-1-butanol reduction product.[6] From the molar refraction it was estimated that about 80% of this material was in the Schiff base form. The infrared spectrum showed a moderately strong C=N absorption at 6.02μ.

Since the nitrosation of 2-propyl-4-ethyloxazolidine using aqueous sodium nitrite and acetic acid had already been reported,[6] this reaction was applied to the latter two anhydro products. 2-Benzylideneamino-1-butanol afforded an 80% yield of benzaldehyde as well as 38% of 2-propyl-3-nitroso-4-ethyloxazolidine. Similarly, nitrosation of 2-(2-ethylhexylideneamino)-1-butanol yielded 2-ethylhexanal (64%) and 2-propyl-3-nitroso-4-ethyloxazolidine. It was evident that the Schiff bases had hydrolyzed in the aqueous media and that the resulting 2-amino-1-butanol underwent deamination, rearrangement and nitrosation to the previously reported N-nitrosoöxazolidine.[7] It was

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[1] Brown University Fellow 1952–1953.

[2] E. D. Bergmann, E. Zimkin and S. Pinchas, *Rec. trav. chim.*, **71**, 168 (1952).

[3] G. E. McCasland and E. C. Horswill, THIS JOURNAL, **73**, 3923 (1951).

[4] H. Heusser, P. Th. Herzig, A. Furst and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

[5] R. A. Henry and W. M. Dehn, THIS JOURNAL, **71**, 2297 (1949).

[6] H. R. Nace and E. P. Goldberg, *ibid.*, **75**, 3646 (1953).

[7] H. R. Nace and M. Gollis, *ibid.*, **74**, 5189 (1952).

further obvious from this work that aqueous media were to be avoided because of the ease of hydrolysis of the anhydro products.

The use of nitrosyl chloride as a nitrosating agent has been reported by Solonina.[8] He obtained nitrosamines from secondary amines using nitrosyl chloride in pyridine. More recently Newman[9] applied this method to the nitrosation of oxazolidones. Since this reagent lends itself to use in anhydrous basic solution, its applicability to the present problem appeared likely. A nitrosation procedure was developed which involved the distillation of nitrosyl chloride into a cold ether–pyridine solution of the anhydro compound. When applied to the nitrosation of 2-propyl-4-ethyloxazolidine, a 54% yield of 2-propyl-3-nitroso-4-ethyloxazolidine was obtained. This was twice the yield afforded by the aqueous method.

2-Benzylideneamino-1-butanol, with nitrosyl chloride, yielded the pale yellow 2-phenyl-3-nitroso-4-ethyloxazolidine (46%). From 2-(2-ethylhexylideneamino)-1-butanol there was obtained a 76% yield of the pale yellow 2-(3-heptanyl)-3-nitroso-4-ethyloxazolidine. Both of these new N-nitroso-oxazolidines were hydrolyzed by 2,4-dinitrophenylhydrazine reagent,[10] with the evolution of gas, to give the 2,4-dinitrophenylhydrazones of the aldehydes from which they were derived (benzaldehyde and 2-ethylhexanal). They were further characterized by infrared spectra (no functional group absorption) and molar refraction. The fact that no C=N absorption was found in the spectra precluded the possibility of a nitrite–Schiff base structure.

The nitrosation procedure used here appears to be by far the best method for nitrosating the anhydro compounds because most side reactions have been eliminated (particularly hydrolysis and deamination of the resulting aminoalcohol). It also seems likely that this method would be applicable to the nitrosation of acid sensitive structures such as ethylenimines.

The course of the above nitrosation reactions is in agreement with most of the reported reactions of anhydro products and clearly indicates that an isomerization or equilibrium shift, from Schiff base to oxazolidine, must occur.[11]

Further evidence was obtained by means of reactions involving α-naphthyl isocyanate and phenyl isothiocyanate. Henry and Dehn[5] reported the preparation of the α-naphthylurea of 2-phenyl-4-ethyloxazolidine. Since their starting material was actually 2-benzylideneamino-1-butanol, there existed the possibility that this product was the Schiff base α-naphthylurethan. In this latter event the derivative should possess infrared absorption characteristic of the C=N bond. The compound was prepared according to the procedure of Henry and Dehn[5] and its infrared spectrum showed only the C=O absorption at 6.00 μ (no C=N at 6.11 μ), hence the oxazolidine structure was confirmed. Similarly, 2-(2-ethylhexylideneamino)-1-butanol reacted with α-naphthyl isocyanate to give the α-naphthylurea of 2-(3-heptanyl)-4-ethyloxazolidine.

The use of a reagent that would react with an NH group and not with an OH group, such as an isothiocyanate, was desirable as added proof of the ready isomerization of the Schiff base forms. When phenyl isothiocyanate and 2-benzylideneamino-1-butanol were mixed in dry ether and allowed to stand, the phenyl thiourea of 2-phenyl-4-ethyloxazolidine was obtained. It had no C=N infrared absorption. 2-(2-Ethylhexylideneamino)-1-butanol also reacted with phenyl isothiocyanate to give the phenyl thiourea of 2-(3-heptanyl)-4-ethyloxazolidine.

These latter reactions are further conclusive evidence for the isomerization of the Schiff bases, particularly so in view of the specificity of phenyl isothiocyanate, under the conditions used, for the amino group. It is also indicated that isocyanates and isothiocyanates can be useful in the derivatization of anhydro products since crystalline compounds are obtained in many cases and anhydrous reaction conditions may be maintained.

On the basis of the reactions reported here, and in previous works, there can be little doubt that aminoalcohol–aldehyde anhydro products, regardless of structure, react with H replacing reagents in anhydrous media to give derivatives of the oxazolidine form. The use of reactions which would involve only the C=N bond and not the secondary amino group has not been studied (for lack of obviously suitable reactions[12]).

Experimental[13]

2-Propyl-4-ethyloxazolidine.—This oxazolidine was prepared as previously described.[6]

(a) **Reaction with Nitrosyl Chloride.**—A flask equipped with a thermometer, stirrer, drying tubes, gas inlet tube and an ice-bath was charged with 14.3 g. (0.1 mole) of freshly prepared 2-propyl-4-ethyloxazolidine, 20 ml. of dry pyridine and 75 ml. of dry ether. The temperature was kept below 7° while 7.2 g. (0.1 mole[14]) of nitrosyl chloride was allowed to distil into the reaction mixture. A white precipitate formed during the addition of the nitrosyl chloride. The reaction mixture was stirred for 20 minutes at

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[8] W. Solonina, *J. Russ. Phys. Chem. Soc.*, **30**, 449 (1898); *Chem. Zentr.*, **69**, II, 888 (1898).

[9] M. S. Newman and A. Kutner, THIS JOURNAL, **73**, 4199 (1951).

[10] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

[11] The single contradictory example reported by Bergmann[3] may not actually constitute a contradiction since it has been demonstrated that in the case of 2-propyl-4-ethyloxazolidine at least, the benzoylation products largely depend upon the age of the sample benzoylated.[5] The fresh material gave rise only to the N-benzoyloxazolidine whereas an older sample yielded both this product and the N,O-dibenzoylated aminoalcohol. It is therefore possible that Bergmann's material was not pure and that the N-anisoylated oxazolidine was formed, with the N,O-dibenzoyl aminoalcohol, but not isolated.

[12] Attempts to add cyclopentadiene to 2-benzylideneamino-1-butanol, in a diene-type synthesis, were unsuccessful. The various reaction conditions tried included: room temperature in benzene and in dry methanol, refluxing in benzene and heating with toluene at 120° in a sealed tube.

The addition of sodium bisulfite to 2-benzylideneamino-1-butanol, according to the method of Knoevenagel, *Ber.*, **37**, 4073 (1901), was also attempted and gave the bisulfite addition product of benzaldehyde rather than that of the Schiff base.

[13] Melting points are corrected; boiling points are uncorrected. The infrared spectra were determined with a double beam spectrophotometer, described by D. F. Hornig, G. E. Hyde and W. A. Adcock, *J. Optical Soc. Am.*, **40**, 497 (1950), using a sodium chloride prism. Liquid film samples, formed by pressing between polished calcium fluoride plates, were used. Microanalyses were performed by Mr. S. M. Nagy and associates, Microchemical Laboratory, Massachusetts Institute of Technology, Cambridge, Mass.

[14] The nitrosyl chloride was considered to be 90% pure.

5° and 100 ml. of cold water was then added. The ether layer was separated and combined with two 50-ml. ether extracts of the aqueous layer. The ether solution was washed with 50 ml. of saturated sodium bicarbonate solution, 50 ml. of water, dried over magnesium sulfate and the ether distilled. The residue was distilled through a 50-mm. Vigreux column to yield 9.3 g. (54%) of 2-propyl-3-nitroso-4-ethyloxazolidine; b.p. 80–82° (0.5 mm.), n^{25}D 1.4600. The nitroso compound was characterized by its infrared spectrum.[7]

2-Benzylideneamino-1-butanol.—A solution of 17.8 g. (0.2 mole) of 2-amino-1-butanol and 21.2 g. (0.2 mole) of benzaldehyde in 150 ml. of benzene was refluxed under a constant water separator for 2.5 hours. The solvent was removed under reduced pressure and the residue was distilled through a 200-mm. Vigreux column to yield 30.0 g. (85%) of 2-benzylideneamino-1-butanol, b.p. 105–113° (0.15 mm.). An analytical sample was prepared by distillation to constant refractive index; b.p. 103–104° (0.05 mm.), n^{25}D 1.5470, d^{25}_4 1.0192, *M*D 55.14, calcd. 53.94; infrared spectrum 3.14 μ (strong, OH stretch), 6.16 μ (v. strong; conjugated C=N stretch), 9.54 μ (strong, OH deformation).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.37; H, 8.76; N, 8.17.

(a) Reaction with Aqueous Sodium Nitrite and Acetic Acid.—The nitrosation procedure described previously for 2-propyl-4-ethyloxazolidine[6] was used. From 8.85 g. (0.05 mole) of the Schiff base, 3.6 g. (0.06 mole) of acetic acid, 4.5 g. (0.065 mole) of sodium nitrite and 75 ml. of water, two fractions were obtained (by distilling the ether extract through the semi-micro column[15]). The first, benzaldehyde, weighed 3.7 g. (80%) and had b.p. 35–42° (0.3–0.4 mm.), n^{25}D 1.5399. The orange-yellow 2,4-dinitrophenylhydrazone melted at 236.5–238°, mixed m.p. with the 2,4-dinitrophenylhydrazone of benzaldehyde (m.p. 236–238°) 236.5–238°. The second fraction, 2-propyl-3-nitroso-4-ethyloxazolidine, weighed 1.6 g. (38%) and was characterized by the infrared spectrum (weak C=O absorption at 5.80 μ indicated some contamination by benzaldehyde); b.p. 72–74° (0.1 mm.), n^{25}D 1.4621.

(b) Reaction with Nitrosyl Chloride.—The procedure described above was employed with 25.2 g. (0.14 mole) of 2-benzylideneamino-1-butanol, 10.5 g. (0.145 mole) of nitrosyl chloride, 30 ml. of dry pyridine and 125 ml. of dry ether. The temperature was kept below 5°. The washed and dried ether extract was distilled through a 200-mm. Vigreux column under reduced pressure to yield 13.4 g. (46%) of the pale yellow 2-phenyl-3-nitroso-4-ethyloxazolidine; b.p. 129–135° (1–2 mm.). Redistillation through the semi-micro column[15] afforded an analytical sample; b.p. 117–118° (0.35 mm.), n^{25}D 1.5375, d^{25}_4 1.1335, *M*D 56.80, calcd. 56.72; infrared spectrum: no functional group absorption.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.29; H, 6.85; N, 13.82.

Addition of the nitroso compound to 2,4-dinitrophenylhydrazine reagent[10] resulted in the evolution of gas[16] and the formation of an orange-yellow 2,4-dinitrophenylhydrazone; m.p. 235.5–238°, mixed m.p. with the 2,4-dinitrophenylhydrazone of benzaldehyde (m.p. 236–238°) 235.5–238°.

(c) Reaction with α-Naphthyl Isocyanate.—According to the procedure of Henry and Dehn[5] 1.0 g. (0.006 mole) of 2-benzylideneamino-1-butanol and 0.7 g. (0.004 mole) of α-naphthyl isocyanate were mixed in 10 ml. of dry ether. After standing 12 hours, the solvent was removed on a steam-bath and 1.2 g. (86%) of the α-naphthylurea of 2-phenyl-4-ethyloxazolidine was obtained. After two recrystallizations from absolute ethanol the m.p. was 132–133° (reported[5] m.p. 133°); infrared spectrum: Nujol mull, 3.07 μ (weak, NH stretch), 6.01 μ (strong, C=O stretch).

(d) Reaction with Phenyl Isothiocyanate.—Three grams (0.018 mole) of 2-benzylideneamino-1-butanol and 2.1 g. (0.016 mole) of phenyl isothiocyanate were mixed in 25 ml. of dry ether. After standing 12 hours, the ether was removed on a steam-bath and the residue was taken up in hot ethanol–water. Cooling yielded 4.65 g. (93%) of the phenylthiourea of 2-phenyl-4-ethyloxazolidine. The m.p. was 101.5–103°[17] after two recrystallizations from ethanol–water; infrared spectrum: Nujol mull, 3.25 μ (weak, NH stretch), 6.23 μ (medium; C=S stretch).

Anal. Calcd. for $C_{18}H_{20}N_2OS$: C, 69.20; H, 6.45; N, 8.97. Found: C, 68.70; H, 6.53; N, 8.59.

2-(2-Ethylhexylideneamino)-1-butanol.—A solution of 17.8 g. (0.2 mole) of 2-amino-1-butanol and 25.6 g. (0.2 mole) of 2-ethylhexanal in 200 ml. of benzene was refluxed for 3.5 hours under a constant water separator. The solvent was removed under reduced pressure and the residue was distilled through a 200-mm. Vigreux column to yield 33.3 g. (84%) of 2-(2-ethylhexylideneamino)-1-butanol, b.p. 84–91° (0.1 mm.). Redistillation afforded an analytical sample; b.p. 77–79° (0.05 mm.), n^{25}D 1.4520, d^{25}_4 0.8743, *M*D 61.56, calcd. for Schiff base 62.17, calcd. for oxazolidine 60.68. Infrared spectrum: same as previously reported.[6]

Anal. Calcd. for $C_{12}H_{25}NO$: C, 72.30; H, 12.64; N, 7.03. Found: C, 72.09; H, 12.56; N, 7.06.

(a) Reaction with Aqueous Sodium Nitrite and Acetic Acid.—As described for 2-benzylideneamino-1-butanol, 15.1 g. (0.075 mole) of 2-(2-ethylhexylideneamino)-1-butanol was nitrosated and yielded 6.1 g. (64%) of 2-ethylhexanal, b.p. 25–33° (4 mm.), and 4.5 g. of impure 2-propyl-3-nitroso-4-ethyloxazolidine, b.p. 85–95° (4 mm.). The n^{25}D of the latter ranged from 1.4506 to 1.4555 and the medium C=O band in the infrared spectrum indicated contamination by the aldehyde. When added to 2,4-dinitrophenylhydrazine reagent,[10] the 2,4-dinitrophenylhydrazone of *n*-butyraldehyde was obtained; m.p. 119.5–121°, mixed m.p. with an authentic sample of *n*-butyraldehyde 2,4-dinitrophenylhydrazone (m.p. 121–122.5°) 121–122.5°.

(b) Reaction with Nitrosyl Chloride.—The procedure used above was employed with 35.8 g. (0.18 mole) of 2-(2-ethylhexylidineamino)-1-butanol, 12.5 g. (0.17 mole) of nitrosyl chloride, 45 ml. of dry pyridine and 200 ml. of dry ether. The temperature was maintained below 0°. The resulting washed and dried ether solution was distilled at reduced pressure through a 200-mm. Vigreux column to yield 31.0 g. (76%) of the yellow 2-(3-heptanyl)-3-nitroso-4-ethyloxazolidine; b.p. 118–122° (2 mm.), n^{25}D 1.4640. An analytical sample was obtained by redistillation through the semi-micro column[15]; b.p. 104–105° (0.4 mm.), n^{25}D 1.4640, d^{25}_4 0.9722, *M*D 64.79, calcd. 65.29; infrared spectrum: no functional group absorption.

Anal. Calcd. for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.27. Found: C, 63.27; H, 10.52; N, 11.97.

When this nitroso compound was added to 2,4-dinitrophenylhydrazine reagent,[10] gas[16] was evolved and the 2,4-dinitrophenylhydrazone of 2-ethylhexanal precipitated, m.p. 117–118.5°, mixed m.p. with an authentic sample of 2-ethylhexanal 2,4-dinitrophenylhydrazone (m.p. 116.5–118°) 116.5–117.5°.

(c) Reaction with α-Naphthyl Isocyanate.—Three grams (0.015 mole) of 2-(2-ethylhexylideneamino)-1-butanol and 2.1 g. (0.012 mole) of α-naphthyl isocyanate were mixed in 20 ml. of dry ether. After standing 12 hours, the ether was removed on a steam-bath and the residue was taken up in 10 ml. of hot ethanol and cooled. The resulting oil solidified to give 4.0 g. (91%) of the α-naphthylurea of 2-(3-heptanyl)-4-ethyloxazolidine, m.p. 124.5–126° after two recrystallizations from ethanol.

Anal. Calcd. for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75; N, 7.60. Found: C, 75.01; H, 8.74; N, 7.52.

(d) Reaction with Phenyl Isothiocyanate.—Three grams (0.015 mole) of 2-(2-ethylhexylidineamino)-1-butanol and 2.1 g. (0.016 mole) of phenyl isothiocyanate were mixed in 20 ml. of dry ether and allowed to stand 12 hours. The ether was removed on a steam-bath and the residue was taken up in hot ethanol and cooled. The resulting oil solidified to yield 3.2 g. (64%) of the phenylthiourea of 2-(3-heptanyl)-4-ethyloxazolidine. After two recrystallizations from ethanol–water, the m.p. was 62.5–64.5°.

Anal. Calcd. for $C_{19}H_{30}N_2OS$: C, 68.22; H, 9.04; N, 8.38. Found: C, 67.93; H, 9.02; N, 8.70.

PROVIDENCE, RHODE ISLAND

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(15) C. W. Gould, Jr., G. Holzman and C. Niemann, *Anal. Chem.*, **20**, 361 (1948).

(16) This gas had the pungent odor of nitrous fumes and colored starch–iodide paper blue.

(17) The m.p. of the phenylthiourea of 2-amino-1-butanol (prepared in ether by the above procedure. *Anal.* Calcd. for $C_{11}H_{16}N_2OS$: C, 58.90; H, 7.19; N, 12.49. Found: C, 58.88; H, 7.17; N, 12.46) was 102–103.5°. A mixed m.p. with the compound obtained from 2-benzylideneamino-1-butanol was depressed to 88–97°.