time 14 was consumed (by tlc). The resulting purple solution was concentrated *in vacuo* to a syrup and the syrup was chromatographed on silica gel to yield in order of elution 20 mg (4%) of 7 (CH_2Cl_2–EtOAc, 2:1 v/v, as eluent), 150 mg (23%) of 16 (CH_2Cl_2–Me_2CO, 6:1 v/v, as eluent), and *ca.* 100 mg of purple syrup (Me_2CO eluent) which was discarded.

One recrystallization of 16 from methylcyclohexane provided yellow needles: mp 234–235°; mass spectrum (70 eV) *m/e* (rel intensity) 512 (20) (M^+), 434 (100) (M − pyridyl), 360 (30); nmr ($CDCl_3$) δ 1.40 (d of t, 6, phosphonate methyls), 2.42 (s, 3, 2-Me), 2.87 (d, 3, J = 2 Hz, 7-Me), 4.23 (m, 4, phosphonate $-CH_2-$), 6.56–7.53 (m, 8), 7.56 (d, 1, J = 9 Hz, H-10), 8.06 (d of m, 1, pyridyl H-6), 8.11 (d of m, 1, pyridyl H-6), 8.78 (d, 1, J = 9 Hz, H-9).

Anal. Calcd for $C_{30}H_{29}N_2O_4P$: C, 70.4; H, 5.7; N, 5.5. Found: C, 70.0; H, 6.1; N, 5.3.

By an analogous procedure, starting with 14 (deuterio), the 6-deuterio derivative was obtained, mass spectrum (70 eV) *m/e* (rel intensity) 513 (23) (M^+), 435 (100) (M − pyridyl), 361 (35).

Isoxazoline 17.—A mixture of 4a (800 mg, 2.0 mmol) and sodium methoxide (800 mg) in 50 ml of methanol was heated at reflux for 30 min, until the starting material had disappeared (tlc). The resulting orange solution was concentrated to dryness, and the residue was chromatographed on Florisil using CH_2Cl_2–Me_2CO–MeOH (5:5:1, v/v) as eluent. The single orange zone was eluted and concentrated to a syrup which crystallized. One recrystallization from CH_2Cl_2–ligroin (bp 35°) gave 530 mg (62%) of analytically pure 17 as reddish orange needles: mp 202–210° dec; uv max (MeOH) 264 nm (log ε 4.47), 355 (3.90), 480 (4.13); mass spectrum (70 eV) *m/e* (rel intensity) 422 (46%) (M^+), 407 (1) (M − Me), 391 (1) (M − OCH_3), 363 (1) (M − CO_2CH_3), 344 (100) (M − pyridyl), 335 (6), 284 (7), 270 (6), 256 (3), 254 (4), 242 (4), 241 (5), 167.5 (5), 78 (3), 59 (1); nmr ($CDCl_3$) δ 2.04 (d, 3, J = 2 Hz), 2.28 (d, 3, J = 1 Hz), 3.44 (s, 3), 6.56–7.73 (m, 9), 8.09 (d of m, 1), 8.42 (d of m, 1), 9.88 (d of m, 1).

Anal. Calcd for $C_{27}H_{22}N_2O_3$: C, 76.8; H, 5.2; N, 6.6. Found: C, 76.5; H, 5.3; N, 6.9.

Conversion of 17 to 18.—A solution of 120 mg of 17 in 12.5 ml of 2 *N* HCl was heated at reflux for 3 hr, concentrated to a syrup, and then redissolved in 10 ml of water. The yellow crystals which separated from solution over a 1-hr period proved identical with the hydrochloride of 18 in every respect.

Isoxazoline 18.—A suspension of 800 mg (2.0 mmol) of 4a in 20 ml of methanol and 40 ml of water containing 1.40 g of sodium hydroxide went into solution over a 30-min period at 60° to give an orange solution. The solution was filtered and slowly acidified with 5% HCl, producing an amphoteric, orange, crystalline precipitate. The solid was redissolved with the addition of another 2 ml of 5% HCl and the resulting yellow solution was refrigerated at 5° for 2 hr, during which time 0.84 g (96%) of light yellow crystals of 18, as the hydrochloride salt, separated. This sample initially dissolved readily in 15 ml of methanol, but within 5 min yielded a relatively insoluble yellow crystalline methanol solvate: mp 187–190° dec; uv max (CH_3OH) 261 nm (log ε 4.54), 360 (3.96), 418 (3.76), 480 (4.20); nmr (CD_3OD) δ 2.32 (d, J = 2 Hz, 3), 2.52 (d, J = 1 Hz, 3), 6.82–7.96 (m, 8), 8.30–8.62 (m, 2), 9.22 (d of m, 1), 9.41 (d of m, 1).

Anal. Calcd for $C_{26}H_{21}ClN_2O_3 \cdot CH_3OH$: C, 68.0; H, 5.2; N, 5.9; Cl, 7.5. Found: C, 67.6; H, 5.2; N, 5.8; Cl, 7.7.

Conversion of 18 to 17.—A sample (200 mg) of the above product (18) in 20 ml of 5% methanolic HCl was heated at reflux for 2 hr, cooled, and basified with 5% $NaHCO_3$, yielding an orange, crystalline precipitate. This product, after purification by Florisil chromatography and recrystallization from CH_2Cl_2–ligroin (bp 35°), proved to be identical in every respect with 17.

Conversion of 18 to 6a.—A mixture of 200 mg of 18 in 10 ml of acetic anhydride was refluxed for 2 min, concentrated to a syrup, and then dissolved in 5% $NaHCO_3$. Yellow crystals of 6a (180 mg) immediately separated upon the addition of aqueous $NaClO_4$ solution.

Registry No.—**4a**, 37387-76-1; **4b**, 37413-08-4; **5**, 37413-09-5; **6a**, 37420-75-0; **6b**, 37413-10-8; **7**, 37387-77-2; **8**, 37387-78-3; **9**, 37387-79-4; **10**, 37387-80-7; **11**, 37387-81-8; **12**, 37387-82-9; **13**, 37387-83-0; **14**, 37387-84-1; **16**, 37387-85-2; **17**, 37387-86-3; **18**, 37387-87-4.

Acknowledgment.—We wish to thank Dr. J. C. Chang for supplying the electrochemical data and Mr. Larry Costa for some of the uv data. We are also grateful for their helpful discussions regarding their interpretations of the data.

Lead Tetraacetate and Pyridine. New, Mild Conditions for a Hofmann-Like Rearrangement. A New Synthesis of 2-Oxazolidinones

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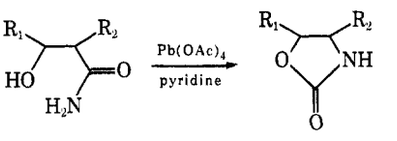
Lead tetraacetate in pyridine has been found to provide a new, mild procedure for effecting a rapid, high-yield, Hofmann-like rearrangement of β-hydroxy primary amides to 2-oxazolidinones. These products in turn give the corresponding β-hydroxy amines so that the reaction can also be used to transform primary amides to amines in high yield.

2-Oxazolidinones have been found useful as drugs and polymer monomers and as such they have attracted considerable attention.[2,3] Not unexpectedly, there are many methods available for their synthesis.[2-4] We would like to report that the reaction of β-hydroxy amides with lead tetraacetate in pyridine constitutes yet another synthetic route to these compounds (eq 1).



(1)

Lead tetraacetate is known to react with primary amides to give isocyanates in a Hofmann-like reaction.[5-7] Typically these reactions are run at 50–60°

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(2) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, pp 396–402.

(3) M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197 (1967).

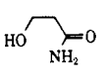
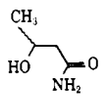
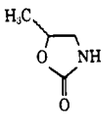
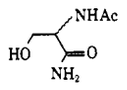
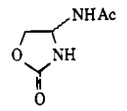
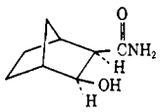
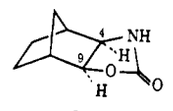
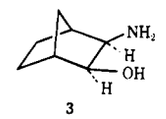
(4) J. E. Herweh and W. J. Kauffman, *Tetrahedron Lett.*, 809 (1971).

(5) J. B. Aylward, *Quart. Rev., Chem. Soc.*, **25**, 407 (1971).

(6) H. E. Baumgarten and A. Staklis, *J. Amer. Chem. Soc.*, **87**, 1141 (1965).

(7) B. Acott, A. L. J. Beckwith, A. Hassanali, and J. Redmond, *Tetrahedron Lett.*, 4039 (1965); B. Acott, A. L. J. Beckwith, and A. Hassanali, *Aust. J. Chem.*, **21**, 185, 197 (1968).

TABLE I
SYNTHESIS OF 2-OXAZOLIDINONES

Starting material	Product	Registry no.	Yield, %[a]	Mp, °C, of analytical sample[d]
		497-25-6	79	87.2–87.8
		36744-42-0	*b*	*b*
		36744-43-1	73	189.0–189.8
 1	 2	36826-32-1	95[c]	134.8–135.2
	 3	36744-44-2	72 (from 1)	91.0–92.0

[a] Yield after recrystallization or chromatography. [b] A crude yield of ~100% was realized (see footnote 11). The analytically pure product (78%) was obtained after acid–base extractions (see Experimental Section). [c] The ir of the unrecrystallized material was superimposable on the ir of the analytically pure sample. [d] Satisfactory analytical data (±0.29% for C, H, N) were reported for all compounds, Ed.

for 20 min to 2 hr in dimethylformamide,[5] benzene,[6,7] or alcoholic solvent.[7,8] The addition of some pyridine to the reaction was found to increase the rate of product formation.[7] We have found that, when an aliphatic β-hydroxy amide in pyridine is treated with solid lead tetraacetate, a fast (<10 min)[9] reaction occurs at room temperature to give the corresponding 2-oxazolidinone in crude yields of ≥95%.[11] No other organic product was detected by tlc. The yields of recrystallized 2-oxazolidinones (Table I) appear to be as good as or better than those obtained by the existing methods.[3]

The large number of methods available for the preparation of β-hydroxy amides (*e.g.*, *via* the Reformatsky reaction and β-lactones[12]) and their stability compared to some other 2-oxazolidinone precursors (*e.g.*, β-haloamines and isocyanates) are two advantages of this method of preparation. The speed of the reaction and its mild conditions should enable it to be used on β-hydroxy amides containing a wide variety of functional groups. The failure of this reaction with salicyl amide, however, is noteworthy.

From the above results, this procedure also appears to constitute a new, mild Hofmann-like reaction for the conversion of amides to amines with retention of configuration. In a preliminary run, the *cis,exo*-hydroxy amide (**1**) was converted to the *cis,exo*-amino alcohol (**3**) in 72% overall yield. The cis,exo stereochemistry of the amino alcohol **3** was inferred from the known stereochemistry of the hydroxy amide **1** and the observed coupling constant of 7 Hz for the C_4 and C_9 methine hydrogens of the 2-oxazolidinone **2**. This coupling is comparable to the observed $J_{2\text{-endo},3\text{-endo}}$ = 6–7 Hz[13,14] for a series of substituted 2-norbornenols.

While the intermediacy of a nitrene has not been conclusively disproved for the reaction of primary amides with lead tetraacetate, some results indicate that the reaction may proceed *via* a concerted oxidative rearrangement of a tetravalent lead–amide complex.[7] By analogy with the lead tetraacetate reaction of primary amides,[5-7] we assume that the synthesis of 2-oxazolidinones progresses *via* a similar complex and is immediately preceded by the formation of a β-hydroxy isocyanate. The lack of reactivity of two N-substituted hydroxy amides [*N*-(3-hydroxypropyl)benzamide and *N*-methyl-*dl*-3-hydroxybutyramide] in this reaction supports the intermediacy of an isocyanate. Finally, the large rate acceleration of this reaction in pyridine seems to implicate hydrogen abstraction from a tetravalent lead–amide complex as the rate-limiting step. While this oxidative cyclization reaction might provide a route to cyclic carbamates, and possibly cyclic ureas and thiol carbamates, of varying ring size, these possibilities have not been investigated.

(8) In this case the isocyanate was isolated as the carbamate, where the alkoxide of the latter was derived from the solvent alcohol.

(9) When lead tetraacetate[10] is added to dry pyridine in the absence of a β-hydroxy amide, a characteristic dark red color is immediately produced.[10] However, in the reactions described here, this red color does not start to appear, even though a slight excess of the lead tetraacetate is present, until the solution is allowed to stand at room temperature for several hours. Until this point is reached, the reaction solution is a clear yellow. The reactions described in the Experimental Section were shown by tlc to be complete in no more than 10 min. From the nature of the reaction, it would seem that the reaction is over as soon as all the lead tetraacetate has dissolved (~8 min). The dissolution of the solid is thus rate limiting.

(10) R. E. Partch, *Tetrahedron Lett.*, 3071 (1964).

(11) In all the cases examined (three of the four), the ir of the crude product was virtually identical with that of the analytically pure sample.

(12) See W. E. Barnett and J. C. McKenna, *Tetrahedron Lett.*, 2595 (1971), and references cited therein.

(13) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963).

(14) R. R. Fraser and Y. S. Lin, *Can. J. Chem.*, **46**, 801 (1968).

Experimental Section[15]

No attempt has been made to maximize the yields of the reactions reported below.

β-Hydroxypropionamide.—Commercially available, crude β-hydroxypropionamide (K & K) was purified by extracting it with acetonitrile. Evaporation and two recrystallizations of the residue from warm acetonitrile gave reasonably pure material, mp 62.5–63.8° (lit. mp 65–66°). The ir and mass spectral data for this solid confirmed its structure.

2-Oxazolidinone.—About 5% excess of solid lead tetraacetate (3.40 g, 7.66 mmol) was added to a stirred solution of 0.65 g of β-hydroxypropionamide (7.30 mmol) in 36 ml of dry pyridine at room temperature. This addition is moderately exothermic. After the reaction mixture was stirred for approximately 1 hr (~8 min was required for dissolution of the lead tetraacetate), 4 drops of ethylene glycol was added to decompose any excess $Pb(OAc)_4$. The reaction solution was evaporated *in vacuo* and the residue was dissolved in methylene chloride. The precipitated $Pb(OAc)_2$ was filtered and the product was extracted from the filtrate with water. The aqueous solution was evaporated, the residue was dissolved in methylene chloride, the solid was filtered, and the filtrate was evaporated to give 0.88 g of crude 2-oxazolidinone. Chromatography on Florisil with ethyl acetate gave a 79% yield of product. Recrystallization from tetrahydrofuran afforded the analytical sample: mp 87.2–87.8°; ir (Nujol) ν_{NH} 3260, ν_{CO} 1720, 1245, 1080, 1020, 965, 918 cm^{-1}; mass spectrum *m/e* (rel intensity) 87 (100, P^+), 59 (28, P − CO), 42 (15, ketene); nmr (60 MHz, D_2O) δ 4.5 (m, 3 H, C_5 H, NH as HDO), 3.6 (m, 2 H, C_4 H).

***dl*-5-Hydroxybutyramide.**—To 20 ml (300 mmol) of concentrated ammonium hydroxide in ice was added 3.0 g (34.8 mol) of β-butyrolactone (Aldrich), also at 0°. After having warmed up to room temperature, the solution was treated with methanol and evaporated *in vacuo* to give a liquid. This liquid material was crystallized from hot ethyl acetate (with a hot filtration) to afford 2.89 g (80.5%) of needles, mp 82.9–84.0.[16] The ir and mass spectral data for this solid confirmed its structure.

***dl*-5-Methyl-2-oxazolidinone.**—The usual reaction conditions and work-up were employed. The methylene chloride filtrate was washed with a small volume of water and 1 *N* hydrochloric acid. Back-extraction with four portions of methylene chloride, followed by drying the combined organic fractions ($MgSO_4$) and evaporation *in vacuo*, yielded 105% of product, almost pure by tlc and ir. Attempts to obtain the analytical sample *via* chromatography or distillation, bp 82–85° (0.09 mm) [lit.[3] bp 111–113° (1 mm), 89–90° (0.04 mm)], resulted in loss of material and no purification. Simple acid–base extractions were found sufficient to give 78% of an analytically pure sample with some material still remaining in the aqueous layers.

The analytical sample had ir (neat) ν_{NH} 3300, ν_{CO} 1735, 1478, 1235, 1065, 967, and 770 cm^{-1}; mass spectrum *m/e* (rel intensity) 101 (86, P^+), 86 (9, P − CH_3), 73 (11, P − CO), 56 (37), 45 (100).

4-(*N*-Acetylamino)-2-oxazolidinone.[17]—The standard reaction conditions were used. The viscous residue obtained after evaporation of the solvent *in vacuo* was treated with acetone–methanol. The resulting solid was filtered, the filtrate was evaporated *in vacuo*, and the residue was treated with hot acetonitrile. The solid in the cooled solution was removed and the filtrate, after evaporation *in vacuo* and treatment with benzene–dichloromethane, yielded 100% of crude, solid product. After recrystallization from acetonitrile, a 73% yield of product was obtained (mp of first crop 180–181°). Recrystallization from ethanol was required to obtain the analytical sample: mp 189.0–198.8° (decomposition with evolution of gas); ir (Nujol) ν_{NH} 3300, 3110, $\nu_{amide\ I}$ 1730, $\nu_{amide\ II}$ 1655, 1550, 1227, 1135, 1105, 1025, 930, 705 cm^{-1}; mass spectrum *m/e* (rel intensity) 144 (8%, P^+), 114 (8, P − HCHO), 100 (21, P − CO_2), 86 (26), 60 (27), 43 (100).

***exo*-3-Carbamyl-*exo*-2-norborneol (1).**—Crude oxazinone[18] (mp 97–104°, 10.0 g, 35.4 mmol), prepared by the method of Smith, Speziale, and Fedder,[19] was slurried in 35 ml of acetone and added to a stirred solution at room tempersture of 50 ml of 0.5 *N* NaOH and 20 ml of acetone. The pH of the reaction solution was kept basic by the addition of 1 *N* NaOH. At the end of the addition 130 ml of water was added, the pH was adjusted to about 7.5 (total amount of base added was 35.4 mmol), and the solution was stirred for 30 min. The solution was flash evaporated to give a viscous oil, which was dissolved in 100 ml of acetonitrile. A white solid precipitated and was filtered and extracted with three 100-ml portions of acetonitrile. The combined filtrates were flash evaporated to give 4.64 g of product, mp 132.0–132.8°, after recrystallization from 20 ml of acetonitrile. A second crop, mp 129.8–131.5°, raised the yield to 5.07 g (92%). The analytical sample was obtained after a recrystallization from ethyl acetate with a hot filtration: mp 132.9–133.3°; ir (Nujol) $\nu_{NH,OH}$ 3350 and 3220, ν_{CO} 1650 and 1590 cm^{-1}; mass spectrum *m/e* (rel intensity) 155 (1, P^+), 127 (100, P − CO), 88 (63), 85 (90); nmr (100 MHz, DMSO-d_6) δ 7.15 and 6.80 (broad s, 2 H), 4.99 (d, J = 5 Hz, 1 H), 3.82 (d of d, J = 5, J' = 7 Hz, 1 H), 3.4–0.9 (m, 9–10 H).

Anal. Calcd for $C_8H_{13}NO_2$ (mol wt, 155.19): C, 61.91; H, 8.44; N, 9.03. Found: C, 61.84; H, 8.54; N, 9.11.

Norbornyl[2,3-*d*]2-oxazolidinone (2).—The usual reaction procedure and work-up gave a methylene chloride filtrate that was washed with water and 1 *N* HCl, dried over $MgSO_4$, and evaporated *in vacuo* to give a 95% yield of a tlc-pure, white powder, whose ir spectrum was identical with that of the analytical sample. One recrystallization of this powder from benzene gave the analytical sample: mp 134.8–135.2°; ir (Nujol) ν_{NH} 3220, ν_{CO} 1725 cm^{-1}; nmr (60 MHz, $CDCl_3$) δ 6.63 (broad s, 1 H, NH), 4.42 (d, J = 7 Hz, 1 H, C_9 H), 3.60 (d, J = 7 Hz, 1 H, C_4 H), 2.38 (broad s, 1 H, C_8 H), 2.17 (broad s, 1 H, C_5 H), 1.9–0.9 (m, 6 H); mass spectrum *m/e* (rel intensity) 153 (73, P^+), 87 (77), 67 (100).

***exo*-3-Amino-*exo*-2-norborneol (3).**—To 0.326 g (2.13 mmol) of crude, unrecrystallized norbornyl[2,3-*d*]2-oxazolidinone was added a solution of 0.34 g (8.51 mmol) of sodium hydroxide in 2.29 ml of water and 4.58 ml of absolute ethanol.[20] After 5 hr of refluxing, the reaction mixture was evaporated *in vacuo* and the residue was partitioned in methylene chloride–water. After two further extractions with methylene chloride, drying ($MgSO_4$), and evaporation *in vacuo*, 0.28 g (103%) of a white powder was obtained. Recrystallization from *n*-hexane gave, in two crops, 0.235 g (87% yield) of the amino alcohol, mp 90.0–90.8°. One final recrystallization from *n*-hexane gave the analytical sample: mp 91.0–92.0°; ir (Nujol) $\nu_{NH_2,OH}$ 3330, 3080, 2750 (broad), 1570, 1080, 813 cm^{-1}; mass spectrum *m/e* (rel intensity) 127 (51, P^+), 98 (82), 70 (59), 56 (100), 43 (67).

Registry No.—**1**, 36744-45-3; lead tetraacetate, 546-67-8; pyridine, 110-86-1.

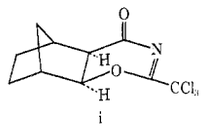
Acknowledgments.—The author wishes to thank Professor F. H. Westheimer for his help and encouragement, Professor James D. White and Dr. John M. McCall for their helpful discussions, Dr. James K. Whitesell for obtaining the 100-MHz nmr spectra, and Dennis K. Rohrbaugh for running all the mass spectra. He also wishes to acknowledge with gratitude Grant No. 30965X from the National Science Foundation to Professor F. H. Westheimer that made this work possible.

(15) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were not corrected. A Perkin-Elmer infrared spectrophotometer Model 137 was used to obtain the ir spectra. Nmr spectra were run using Varian T-60 and HA-100 spectrometers. Mass spectra were determined on an AEI MS-9 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Scandinavian Microanalytical Laboratory, Denmark.

(16) The melting point given in "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965, is 84–87°.

(17) The starting *N*-acetyl-*dl*-serine amide was obtained from Cyclo Chemical and used without further purification.

(18) The oxazinone i was always contaminated by varying amounts of



i

the amide trichloroacetate[19] resulting from the addition of 1 equiv of water. This material, however, does not complicate the reaction.

(19) L. R. Smith, A. J. Speziale, and J. E. Fedder, *J. Org. Chem.*, **34**, 633 (1969).

(20) C. D. Lunsford, R. P. Mays, J. A. Richman, Jr., and R. S. Murphy, *J. Amer. Chem. Soc.*, **82**, 1166 (1960).