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SYNTHESIS OF HYDROXAMIC ACIDS BY REDUCTIVE REARRANGEMENT OF OXIMINOESTERS

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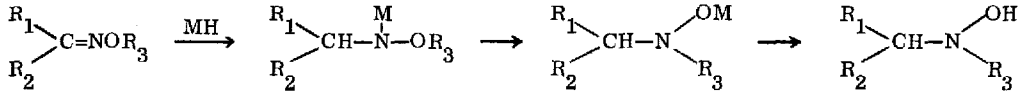
Sir,

Among the members of biologically important peptide derivatives, the oxidized amides known as hydroxamic acids have been found to exhibit unique growth-promoting characteristics in fungi, bacteria and higher plants as a result of their powerful iron-chelating ability. Included are the ferrichromes, ferrirubins, and ferrioxamines. Others such as the aspergillic acids demonstrate high antibiotic activity against gram-negative organisms.[1,2] Our growing interest in the pharmacological importance of hydroxamates and other peptide related substances led us to devise a new synthesis, which we disclose in this letter.

The conceptual basis for our work lay in the differing reactivity of oximes and hydroxylamines towards acylating agents. Since oximes are readily O-acylated whereas hydroxylamines form N-acyl derivatives (hydroxamic acids) as the thermodynamically more stable product,[3,4] we reasoned that reduction of the C=N bond in oximinoesters ought to be attended by an O-to-N acyl shift leading directly to hydroxamic acids (Scheme 1). Application to cyclic oximinolactones would represent a new approach to the synthesis of large-ring hydroxamic acids and, after deoxygenation, macrocyclic lactams.

SCHEME 1



1 2 3 4

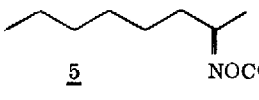
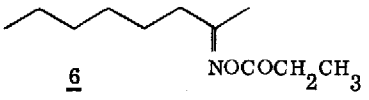
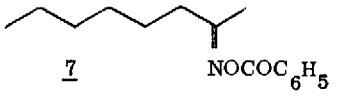
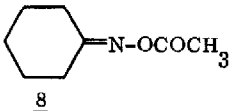
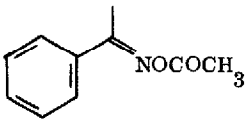
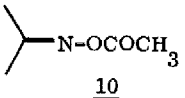
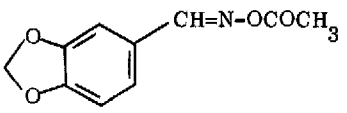
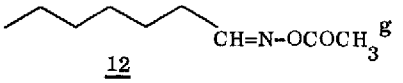
R_1, R_2 = alkyl; R_3 = acyl

Initial results proved unpromising since most reducing agents ($NaBH_4$, Li(sec-butyl)$_3$BH, (isobutyl)$_2$AlH, $LiAlH_4$) preferentially attacked the ester carbonyl.[5] However, Hassner has reported that ketoxime acetates are reduced to amines using an excess of diborane in tetrahydrofuran,[6] presumably by C=N hydroboration and subsequent displacement of acetate. Hoping to interrupt this reduction after the initial hydroboration, 2-octanone ketoxime acetate was exposed to only one mole-equivalent of BH_3 in THF at -78°. Indeed after stirring 6 hr at room temperature and heating the solution overnight at reflux, a 60% yield of N-2-octylacetohydroxamic acid was obtained, identical (ir, nmr, mass spectra) with an authentic sample prepared by standard acetylation of N-2-octylhydroxylamine.[4] A summary of our results clearly delineating the broad scope of this process is formulated in the Table.

A number of simple experimental observations shed some light on the course of this reductive rearrangement. The initial hydroboration is relatively rapid (0° for aldoximinoesters; room temperature for ketoximinoesters) and requires a full mole-equivalent of borane to consume all the starting material. Neither disiamylborane[7] nor thexylborane[8] are sufficiently reactive substitutes. The ensuing rearrangement of intermediate O-acylhydroxylamine-boranes 2 (M=BH_2) is a slower process and necessitates reflux temperatures. We have confirmed this by terminating the reaction with aqueous sodium hydroxide before heating and isolating the corresponding hydroxylamine 2 (R_3=M=H) in most instances. Although the process seems to be general, side reactions involving the two residual hydrogens attached to boron in 3 (M=BH_2) are in part responsible for lowering the yields of hydroxamic acids.[9] Bubbling propene through the reaction mixture before reflux in order to destroy these B-H residues via hydroboration noticeably improves the yield of 4 from 12, but not of hydroxamates derived from ketoximinoesters.

The following experiments demonstrate conclusively that the mechanism by which 2 (M=BH_2) is transformed into 3 involves an intermolecular O-to-N acyl shift. When an equimolar mixture of acetone ketoxime acetate 10 and 2-octanone ketoxime propionate 6 was subjected to the conditions for reductive rearrangement, a 1:1 mixture of N-2-octylacetohydroxamic acid and N-2-octylpropionohydroxamic acid was formed. Using a 2:1 mixture of 10 and 6, the corresponding N-2-octylhydroxamates were detected by glpc analysis (10% SE-30 on Chrom W, 6', 160°) in precisely this

TABLE

Oximinoester[a]	Product (Yield)[b,c]	NMR Spectral Data[d] δ($CDCl_3$)
 5	N-2-octylacetohydroxamic acid (60)[e]	1.11 (d, 3H, J=7), 1.95, (s, 3H), 3.7-4.0 (broad m, 1H)
 6	N-2-octylpropionohydroxamic acid (58)[e]	1.15 (d, 3H, J=7), 2.23 (q, 2H, J=7), 3.9-4.1 (broad m, 1H)
 7	N-2-octylbenzohydroxamic acid (40)[e] m.p. 71-74°	1.30 (d, 3H, J=7), 4.3-4.5 (broad m, 1H), 7.75 (m, 2H), 8.40 (complex m, 3H)
 8	N-cyclohexylacetohydroxamic acid (45) m.p. 105-106°	1.96 (s, 3H), 3.5-3.7 (broad m, 1H)
 9	N-(α-phenethyl)-acetohydroxamic acid (55)	1.41 (d, 3H, J=7), 1.89 (s, 3H), 5.0 (broad q, 1H), 7.27 (s, 5H)
 10	N-isopropylacetohydroxamic acid (45)	1.12 (d, 6H, J=7), 1.96 (s, 3H)
 11	N-(3,4-methylenedioxybenzyl)acetohydroxamic acid (25)[e,f]	1.98 (s, 3H), 4.2 (broad s, 2H), 5.92 (s, 2H), 6.76 (narrow m, 3H; underlying broad s, 1H)
 12	N-heptylacetohydroxamic acid (45)[e]	2.00 (s, 3H), 3.25 (broad q, 2H, J=7)

(a) All oximinoesters were prepared by acylation of the corresponding oximes.
(b) All hydroxamic acids were purified by chromatography on Florisil. Reported yields are for isolated pure compounds. (c) In each instance oximinoester + 1 mole equiv. BH_3 were mixed in THF at -78°, stirred 6-10 hr at room temp., then heated at reflux for 12-18 hr.
(d) In addition to these spectral features, all products showed strong infrared absorptions at 3.0μ (OH) and 6.0-6.1μ (C=O) and gave a characteristic deep red color in aqueous $FeCl_3$. (e) Authentic samples of these substances were synthesized for direct comparison. (f) This substance was unusually unstable and details of its facile thermal decomposition will be reported in Experientia. (g) Propene was bubbled through the solution after 3 hr at room temp. until the ensuing exothermic reaction ceased. The solution was then heated to reflux and completed as usual.

ratio. No change in the product distribution was observed even when these experiments were repeated at a tenfold dilution. This mechanism, although surprising, is in accord with kinetic studies by Jencks on the decomposition of hydroxylamine-O-acetate.[3] Failure of 2 to undergo an apparently facile intramolecular rearrangement seems to indicate little, if any, ionic character to the N-B bond in this first-formed intermediate and in the transition state leading to 3. We are continuing to investigate alternative reducing agents, especially silanes,[10] in an effort to apply this method to the synthesis of cyclic hydroxamic acids and macrocyclic polypeptides; substances whose role as pharmacological effectors deserves further exploration.

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References and Footnotes

(1) J. P. Bapat, D. St. C. Black, R. F. C. Brown, Adv. Heterocyclic Chem., 10, 199 (1969).

(2) (a) J. B. Nielands, Science, 156, 1443 (1967).

(b) A. J. Birch, H. Smith, Ciba Foundation Symp. Amino Acid, Peptide Antimetab. Act., (Little, Brown; Boston, 1958) p. 247.

(3) W. P. Jencks, J. Amer. Chem. Soc., 80, 4581 (1958).

(4) S. R. Sandler, W. Karo, "Organic Functional Group Preparations," Vol. 3, 406 (1972), (Academic Press).

(5) Sodium cyanoborohydride failed to reduce 1, even under forcing neutral or acidic conditions.

(6) A. Hassner, P. Catsoulacos, J. Chem. Soc. Chem. Commun., 590 (1967).

(7) H. C. Brown, B. C. Subba Rao, J. Amer. Chem. Soc., 91, 6423, 6428 (1969).

(8) H. C. Brown, A. W. Moerikofer, J. Amer. Chem. Soc., 85, 2063 (1963).

(9) From the reductive rearrangement of 9 and 11 we have identified the corresponding N-ethyl, N-alkylhydroxylamines as by-products, which must arise from overreduction of the desired acetohydroxamic acids.

(10) I. Ojima, T. Kogure, Tetrahedron Lett., 2475 (1973).