°C; $^{13}C$ NMR ($Me_2SO$-$d_6$) 157.4, 147.7, 38.0, 27.8, 15.7. Anal. Calcd for $C_{10}H_{20}N_6SO_2$: C, 41.67; H, 6.95; S, 11.11. Found: C, 41.79; H, 7.37; S, 10.95.

**Reaction of Bis(3-oxo-1-butyl) Sulfide (2e) with $Na_2S$.** The sulfide **3e** (1.0 g, 57 mmol) was dissolved in 7 mL of dry EtOH, and a small amount of anhydrous $Na_2S$ was added. After 24 h at room temperature, the dark orange solution was diluted with ether, washed with $H_2O$ three times, dried, and evaporated, to leave 0.5 g of an orange oil, which was chromatographed through 14 g of $SiO_2$ with $CHCl_3$ as eluant. The first fraction consisted of 0.28 g (28%) of a yellow oil, identified as the tetrahydrothiopyran-4-ol **21**: IR 3500 (br), 2960, 2920, 2830, 1695, 1460, 1430, 1370, 1350, 1310, 1210, 1150, 1110, 1090, 920, 890; $^1H$ NMR ($CDCl_3$) 3.67 (br, 1 H), 2.23 (s), 1.16 (s), 3.20–0.93 (m); $^{13}C$ NMR, see Table I; mass spectrum 174 (3), 113 (3), 104 (3), 103 (2), 71 (16), 70 (15), 55 (52), 43 (100). Anal. Calcd for $C_8H_{14}SO_2$: C, 55.14; H, 8.10. Found: C, 55.15; H, 7.86.

The second fraction was a yellow oil (0.15 g, 15%) identified as the tetrahydrothiopyran-4-ol **22**: IR 3450, 2820, 1695, 1420, 1350, 1200, 1160, 1135, 1100, 1080, 925; $^1H$ NMR ($CDCl_3$) 2.23 (s), 1.16 (s), 3.08–1.75 (m); mass spectrum 174 (2), 113 (10), 104 (3), 103 (4), 71 (19), 70 (9), 55 (35), 43 (100); $^{13}C$ NMR, see Table I. Anal. Calcd for $C_8H_{14}SO_2$: C, 55.14; H, 8.10. Found: C, 55.08; H, 7.74.

**Acknowledgment.** This research was supported by grants from The Robert A. Welch Foundation and the TCU Research Foundation.

**Registry No. 1a**, 4070-75-1; **1c**, 122-57-6; **1d**, 94-41-7; **1e**, 78-94-4; **2d** (isomer 1), 75731-94-1; **2d** (isomer 2), 75731-95-2; **2e**, 40790-04-3; **3a**, 75731-96-3; **3c**, 23849-67-4; **3d**, 75731-97-4; **3e**, 75731-98-5; **10**, 5076-35-7; **11**, 61138-07-6; **13**, 75731-99-6; **22**, 75732-00-2; $H_2S$, 7783-06-4.

**Supplementary Material Available:** Computer simulated and actual NMR spectra of the ABX and OH portion of **3c** and **3d** (2 pages). Ordering information is given on any current masthead page.

# Synthesis of (*Z*)-4-(Acylamino)- and 4-(Alkylamino)-α-oximinophenylacetic Acids: Properties and Stereochemical Determination

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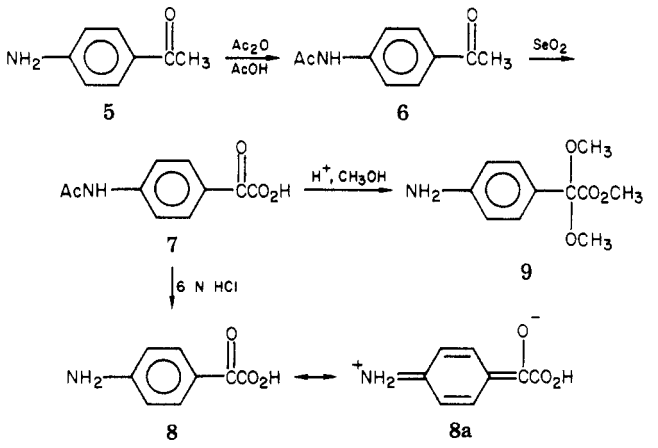
The preparation, properties, and stereochemical determinations of a series of 4-substituted α-oximinophenylacetic acids are described. The 4-acetamido and 4-[[(benzyloxy)carbonyl]amino]-α-oxophenylacetic acids **7** and **19** were synthesized from the corresponding acetophenones with selenium dioxide. The oximes were then prepared and their stereochemistry determined as *Z* (syn), through the chemical properties of the methoxyimino derivatives. A key intermediate was (*Z*)-methyl 4-[[(benzyloxy)carbonyl]amino]-α-[[(tetrahydro-2*H*-pyran-2-yl)oxy]imino]phenylacetate (**24**), which was synthesized from the free oxime or from the keto acid by using *O*-(tetrahydropyran-2-yl)hydroxylamine. Deprotection of this compound at nitrogen gave the 4-amino-α-oximino ester, **25**, which was acylated with a variety of acid chlorides and hydrolyzed to the 4-(acylamino)-α-oximinophenylacetic acids. By employment of methyl 4-amino-α-oxophenylacetate dimethyl ketal (**9**), a general reductive amination process was developed, leading to the 4-(alkylamino)-α-oximinophenylacetic acids.

Many novel and therapeutically significant β-lactam antibiotics have recently been developed containing the (*Z*)-α-oximino acid moiety appended to a β-lactam nucleus.[1] Most notable among these are cefuroxime[2] (**1**), cefotaxime[3] (**2**), and nocardicin A[4] (**3**) (Chart I). In all known cases, the *E* isomers were not found to be active.

Scheme I




As part of our β-lactam program, we were interested in preparing new α-oximino acids of type **4**, which bear a distinct electronic and spatial resemblance to the 4-hydroxy-α-oximinophenylacetic acid portion of **3**. The 4-amino derivative **4**, unlike its 4-hydroxy counterpart, possesses a greater potential for the elaboration of bio-

(1) T. Kamiya, T. Takao, T. Teraji, M. Hashimoto, O. Nakaguti, and T. Oku, German Offen. 2728776 (1978); T. Takaya, T. Masugi, H. Takasugi, and H. Kochi, Japanese Kokai 7783784 (1977); *Chem. Abstr.*, **88**, 22950 (1978); M. C. Cook, G. I. Gregory, and J. Bradshaw, U. S. Patent 4092477 (1977); T. Kamimura, Y. Matsumoto, N. Okada, Y. Mine, M. Nishida, S. Goto, and S. Kuwahara, *Antimicrob. Agents Chemother.*, **16**, 540 (1979).

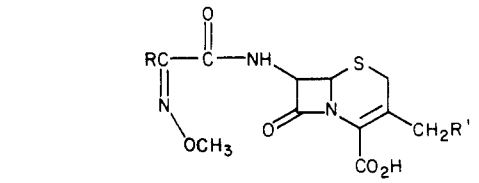
(2) (a) C. H. O'Callghan, R. B. Sykes, R. D. Foord, and P. W. Muggleton, *J. Antibiot.*, **29**, 29 (1976); (b) W. J. Gottstein, G. B. 1557423 (1977); (c) M. C. Cook, G. I. Gregory, and J. Bradshaw, G. B. 1453049 (1976).

(3) M. Numata, I. Minamida, S. Tsushima, T. Nishimura, M. Yamaoka, and N. Matsumoto, *Chem. Pharm. Bull.*, **25**, 3117 (1977); M. Vignau and A. Lutz, German Offen, 2737504 (1978); R. Heymes, A. Lutz, and E. Schrinner, *Infection (Munich)*, **5**, 259 (1977); M. Numata, I. Minamido, and S. Tsushima, German Offen. 2727753 (1978); A. Heymes and A. Lutz, German Offen. 2702501 (1976); R. Bucourt, R. Heymes, A. Lutz, L. Penasse, and J. Perronnet, *Tetrahedron*, **34**, 2233 (1978).

(4) H. Aoki, H. Sakai, M. Kohsaka, T. Konomi, J. Hosoda, Y. Kubochi, E. Ignuchi, and H. Imanaka, *J. Antibiot.*, **29**, 492 (1976); M. Hashimoto, T. Komori, and T. Kamiya, *J. Am. Chem. Soc.*, **98**, 3023 (1976); T. Kamiya, T. Oku, O. Nakaguchi, H. Takeno, and M. Hashimoto, *Tetrahedron Lett.*, 5119 (1978); G. A. Koppel, L. McShane, F. Jose, and R. D. G. Cooper, *J. Am. Chem. Soc.*, **100**, 3933 (1978).

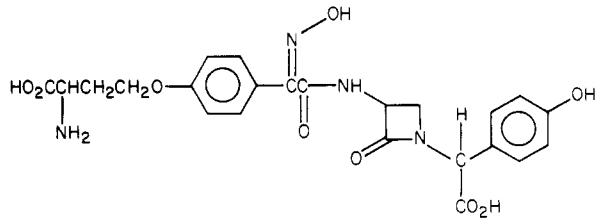
0022-3263/81/1946-0134$01.00/0 

Chart I[a]

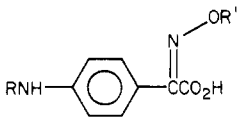


1, R =  ; R′ = $OC(O)NH_2$

2, R =  ; R′ = $OC(O)CH_3$



3



4

[a] R = acyl, alkyl; R′ = H, O-protecting group.

logically stable analogues.[5] We report the synthesis and chemistry of these α-oximino acids, 4, and of the keto acids from which they were derived.

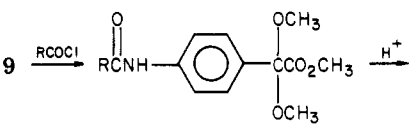
## Results and Discussion

Our initial stategy was to prepare 4-amino-α-oxophenylacetic acid (8), the simplest precursor to 4, which could be derivatized at nitrogen and finally oximated (with the determination of stereochemistry) and protected for coupling. Alternatively, 8 might be oximated first and then derivitized at nitrogen with the stereochemistry of the oxime known and fixed for each new N derivative.

Several methods are available for the preparation of α-oximino acids.[6] Synthesis from the α-keto acids seemed most desirable, since the keto acids themselves possess some biological activity (always less than the oximino acids) when employed as β-lactam side chains.[7] 4-Amino-α-oxophenylacetic acid (8) was readily prepared by the oxidation of 4-acetamidoacetophenone (6) with selenium dioxide,[8] followed by hydrolysis with 6 N hydrochloride acid (Scheme I). Friedel–Crafts acylation of acetanilide with ethyloxalyl chloride also provided 7 in 35% yield, but purification of the product was very difficult, rendering this process less attractive.

The amino acid 8 is a very strong acid ($pK_a$ = 1.5) and resists acylation at the relatively nonbasic nitrogen even under forcing conditions, presumably because of the delocalization of the nitrogen lone pair through the ring (8a). Acylation was accomplished by silylation of 8 and prolonged treatment with an acid chloride. This process was moisture sensitive and not reproducible for large-scale

Scheme II



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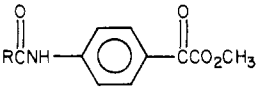
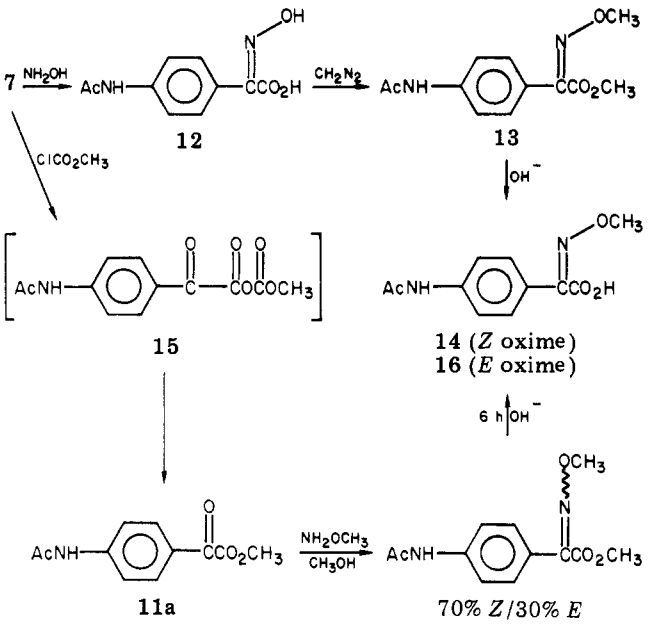


11

Scheme III



preparations. The same delocalization that retarded acylation also impeded clean oximation of the keto function in 8. The acylation problem was circumvented by preparation of the ketal ester 9 from the keto acid 7 with methanol and sulfuric acid. The ketal ester 9, without the delocalization of 8a being possible, was easily acylated under standard conditions and was readily deprotected to the keto esters 11 with perchloric acid (Scheme II).

We soon discovered, however, that oximation of these esters, 11, or their corresponding acids gave mixtures of syn and anti isomers which required tedious separation in each case. Because of this difficulty, oximation of the N-protected keto acid 7 was examined, with the hope that the acetyl group could be subsequently removed, permitting elaboration of the 4-amino substituent, with an oxime of known stereochemistry in place.

4-Acetamido-α-oxophenylacetic acid (7) was oximated at pH 6 with hydroxylamine hydrochloride to give two oximes (92:8 ratio) in quantitative yield (Scheme III). Recrystallization from dioxane gave a single isomer. While the stereochemistry of the α-alkyl oximes has been assigned on the bases of their $^{13}C$ and proton (with shift reagent) NMR spectra,[9] no such correlation could be found in the α-aryl series.[9f] Published reports, however, clearly point to a large chemical variance between the E and Z

(5) Ester derivatives at the p-hydroxyl-α-oximinophenylacetic acid portion of nocardicin A were not active and may be cleaved readily in vivo. T. Kamiya, private communication.

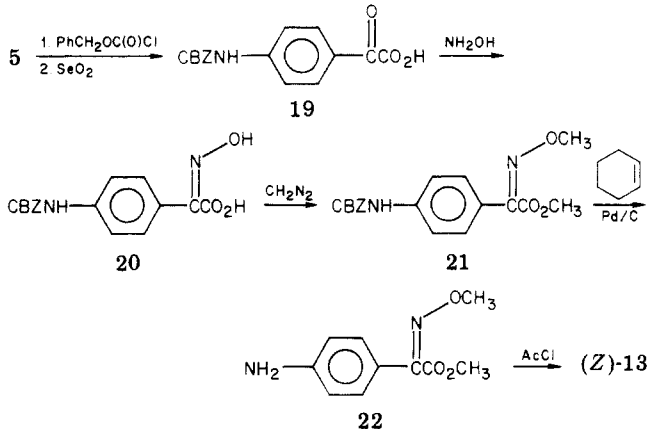
(6) R. H. Barry and W. H. Hartung, *J. Org. Chem.*, **12**, 460 (1947); K. E. Hamlin and W. H. Hartung, *J. Biol. Chem.*, **145**, 349 (1942).

(7) A. G. Long, E. D. Wilson, and W. G. Graham, U.S. Patent 3573294 (1971).

(8) For a review of selenium dioxide oxidations see N. Rubjohn, *Org. React.* **24**, 261 (1976).

(9) (a) D. Berlin and S. Bengaraju, *J. Org. Chem.* **36**, 2912 (1971); (b) Z. W. Wolkowski, *Tetrahedron Lett.*, 825 (1971); (c) B. L. Fox and J. E. Reboulet, *J. Org. Chem.*, **35**, 6234 (1970); (d) C. A. Brunnell and P. L. Fuches, *ibid.*, **42**, 3614 (1977); (e) F. E. Hawkes, K. Hewig, and J. D. Roberts, *ibid.*, **39**, 1017 (1974). (f) A series of E and Z oximes was examined, but no correlation was found. H. D. H. Showalter and P. K. Woo, unpublished results.

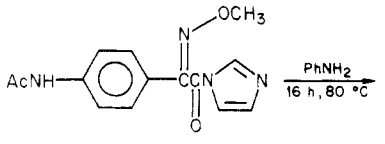
Scheme IV

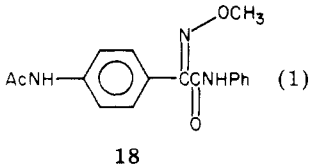



[a] CBZ = $PhCH_2OC(O)$.

isomers of α-oximino acids and esters.[10,11] The most complete data have been compiled for a series of etherified α-oximino esters,[11] where the *Z* (syn) isomers hydrolyze much more slowly than the corresponding *E* (anti) forms. This indirect evidence led to the assignment of stereochemistry in cefuroxime **1**, which was verified unequivocally by X-ray analysis.[2b]

By use of this approach, the keto acid **7** was esterified with methyl chloroformate and triethylamine to give **11a** in quantitative yield by the spontaneous decomposition of the mixed anhydride **15**. Oximation of **11a** with methoxylamine hydrochloride gave a 70:30 mixture of isomeric oximes. When this mixture was subjected to 0.3 equiv of sodium hydroxide for 30 min, a single isomer was selectively obtained as the acid and assigned the *E* (anti) configuration **16**. The remaining portion containing the less reactive, more hindered isomer was hydrolyzed for 6 h to give the (*Z*(*syn*))-oximino acid **14**, uncontaminated with any anti isomer. The isomerically pure acid **12** (from oximation of **7**) was then permethylated with diazomethane followed by hydrolysis to give the *Z* oximino acid (*Z*)-**14**, thus establishing the stereochemistry of **12** and **13** as *Z* also. Additional evidence for this assignment was obtained by the reaction of the imidazolide **17** (prepared from **14** with 1,1′-carbonyldiimidazole) with aniline (eq 1).




This process required 80 °C for 16 h, while the less hindered *E* isomer gave the anilide in 30 min at 0 °C.

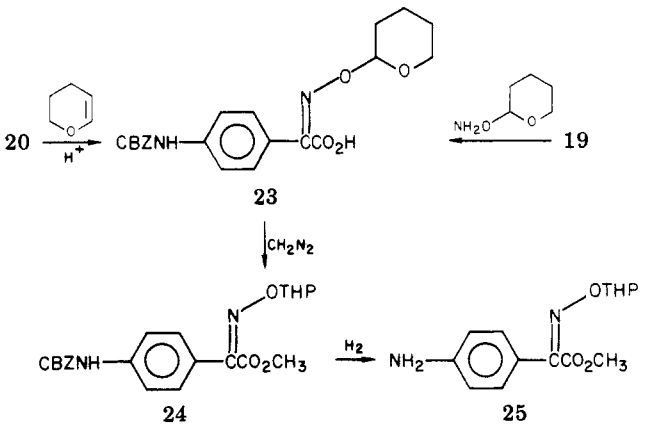
The attempted removal of the acetyl group in **12** or **13** to the free amine with acid or base caused extensive decomposition. This obstacle was overcome by utilizing the (benzyloxy)carbonyl (CBZ) protecting group, which was easily removed by catalytic hydrogenation. 4-[[(Benzyloxy)carbonyl]amino]-α-oxophenylacetic acid (**19**) was prepared just as the 4-acetamido derivative was (Scheme IV). Oximation and crystallization gave a single isomer, **20**, in 82% yield. The stereochemistry of **20** was assigned by conversion to the amino oximino ester **22**, which was acylated to the previously assigned (*Z*)-oximino ester **13**.

Table I. Ratios of *Z* (Syn)/*E* (Anti) Oximes Obtained under Various Oximation Conditions[a]

| α-keto acid or ester | water, 25 °C, pH 6 | water, 50 °C, pH 6 | ethanol, 25 °C | ethanol, 50 °C |
|---|---|---|---|---|
| 7 | 93:7 | 85:15 | 88:12 | 75:25 |
| 19 | 88:12 | 70:30 | 70:30 | 65:35 |
| 11a | not sol | not sol | 80:20 | 70:30 |
| 19 (methyl ester) | not sol | not sol | 70:30 | 59:41 |

[a] Ratios were determined by high-pressure LC.

Scheme V



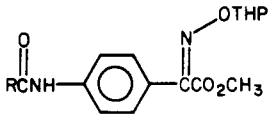

The stereochemistry of the oximation process appeared to be compound dependent. In all the examples we encountered, better syn stereoselectivity was obtained when the oximation was performed on the α-keto acid in water at pH 6. In alcoholic solvent or at higher temperatures the percentage of the anti isomer increased. The α-keto esters were always less stereospecific than the corresponding acids. These observations are summarized in Table I. Oximation with methoxylamine hydrochloride followed the same trends.

We then examined the possibilities for the protection of the oxime. Attempts to directly couple α-oximino acids to β-lactam nuclei were unsuccessful due to their facile decarboxylation under the usual conditions of carboxyl activation.[12] The alkoxyimino acids could be easily coupled, but removal of the *O*-alkyl group could not be effected. Further, only protected oximes could be cleanly acylated at the 4-amino position. Suitable protection was achieved with the tetrahydropyranyl derivative[13] **23**, which was prepared by treatment of the oxime **20** with dihydropyran and acid catalysis or from α-keto acid **19** with *O*-(tetrahydropyran-2-yl)hydroxylamine[14a] with 92% *Z* stereoselectivity (Scheme V). This process was general for many keto acids.[14b] The methyl ester of **23** was prepared with diazomethane, followed by deblocking of the nitrogen protecting group with hydrogen over palladium

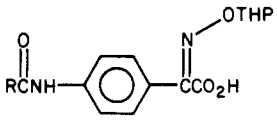
(10) A. Ahmad and I. D. Spenser, *Can. J. Chem.*, **39**, 1340 (1961).
(11) J. Bradshaw and G. B. Webb, U.S. Patent 3903113 (1975).

(12) Use of 1,1′-carbonyldiimidazole, thionyl chloride–DMF, and mixed anhydride formation to activate the carboxyl all led to formation of the corresponding nitrile with rapid loss of $CO_2$ and water. Further details of this work will be published later.
(13) Preliminary work on several model compounds showed that the THP protecting group could be easily removed in the presence of β-lactam nuclei with water and trifluoroacetic acid.
(14) (a) R. N. Warrener and E. N. Cain, *Angew. Chem., Int. Ed. Engl.* **5**, 511 (1966); (b) P. K Woo, manuscript in preparation.

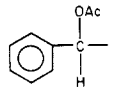
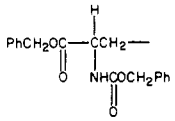
Table II. Preparation of 26 and 27 from 25[d]



26

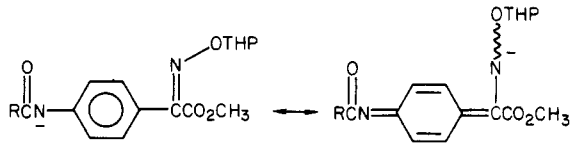


27

| | R | yield[a] of 26, % | yield[a] of 27, % |
|---|---|---|---|
| a |  | 62 | 86 |
| b |  | 85 | 84 |
| c |  | 51 | 90 |
| d | $CF_3$ | 83[b] | 68 |
| e |  | 81 | c |

[a] All yields are for purified materials. [b] Not characterized as the ester, but converted directly to the acid. [c] Hydrolysis to the acid was unsuccessful. [d] Satisfactory analyses (C, H, N) were reported for 26a-c,e and 27a-d.

on carbon to give 25. The intermediate 25 was acylated with a variety of acid chlorides to 26, and the methyl esters were then hydrolyzed by using lithium iodide in boiling pyridine[15] to give the free acids 27 (Table II). With the protected aspartamide derivative, entry 27e, this methodology failed, as competitive hydrolysis of the benzyl groups occurred. When these hydrolyses were performed with alcoholic sodium hydroxide, a 50:50 mixture of isomeric oximino acids 27 was obtained. This result is rationalized by the formation of the acylamino anion 28, which,

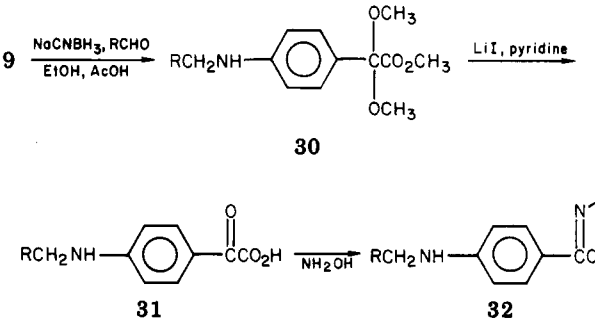


28 29

when delocalized through the ring, lowers the energy barrier for isomerization about the carbon–nitrogen bond of the oxime depicted in 29. Under these same reaction conditions, compounds 22 and 25, with much less acidic N–H protons, showed no such isomerization of the oxime.

With the preparation of the *N*-acyl O-protected oximino acids completed, we turned our attention to the synthesis of the *N*-alkyl derivatives 4 (R = alkyl, $R^1$ = H). The formation of these compounds was a formidable problem, which has only been partially resolved. Direct alkylation of the amine 25 gave a mixture of products, and reductive amination ($NaCNBH_3$ or $H_2$) gave only products in which the oxime had been reduced. By use of methyl 4-amino-α-oxophenylacetate dimethyl ketal (9) and an appropriate aldehyde, reductive amination with $NaCNBH_3$ gave monoalkylated adducts 30 in good yield (Scheme VI). The *N*-benzyl derivative was cleanly deprotected to the keto acid 31a, which was forcibly converted to the oxime 32a with excess hydroxylamine hydrochloride at high temperature (one stereoisomer isolated). The same sequence using 30b, the potential nitrogen isostere of the nocardicin

Scheme VI[a]



30



31 32

[a] a, R = Ph; b, R = $PhCH_2O_2CCH[NHC(O)OCH_2Ph]CH_2$.

A (3) side chain, led to very low yields of 31b which decomposed on oximation.

This reductive amination, performed with several aldehydes and aromatic amines in our laboratory, may be synthetically useful because of very short reaction times, and it does not employ a large excess of amine to ensure monoalkylation,[16] a major drawback where the amine is difficult to prepare or remove.

## Conclusion

The results from this study provide a sound methodology for the synthesis of biologically important α-oximinoarylacetic acids with complex substituents. The oxime of determined stereochemistry must be introduced early with strong electron-releasing groups protected to neutralize their releasing effect. Deblocking of these groups then permits the synthesis of more complex entities. In those cases where this sequence cannot be followed (for the 4-(alkyamino)-α-oxophenylacetic acids), oximation and determination of stereochemistry were very difficult. The tetrahydropyranyl protecting group for the oximes proved valuable for the coupling of these oximino acids to β-lactam nuclei. The facile introduction of this moiety can now be accomplished through two distinct routes.

The coupling of these compounds to β-lactam nuclei and their biological activity will be reported elsewhere.

## Experimental Section

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Digilab FTS-14 or Beckman IR 9 prism grating dispersion instrument. $^1H$ nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 or a Bruker WH-90 instrument. The Bruker WH-90 was modified with a Nicolet Technology Corp. B-NC12 data acquisition system. Chemical shifts are reported as values in parts per million from internal tetramethylsilane. Combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer. $pK_a$ values were determined on a Copenhagen Radiometer TTT 60 titrator.

Column chromatography was carried out by using E. Merck silica gel 60 (70–230 mesh, ASTM). Tetrahydrofuran was distilled from $NaAlH_4$ and pyridine and dioxane from $CaH_2$. Diazomethane was prepared by using the Diazald kit from Aldrich. 4-Aminoacetophenone was obtained from Eastman.

Solutions were dried with magnesium sulfate and concentrated on a rotary evaporator at 30–43 °C at pressures of 5–20 mmHg.

**4-Acetamido-α-oxophenylacetic Acid (7).** To 20.0 g (0.112 mol) of 4-acetamidoacetophenone[17] in 200 mL of pyridine (65 °C) was added 18.8 g (1.5 equiv) of selenium dioxide in three portions, and the mixture was stirred for 3 h at 100 °C. Filtration and concentration gave an oil that was dissolved in 5% NaOH and

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(16) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, 93, 2897 (1971); K. A. Schellenberg, *J. Org. Chem.*, 28, 3259 (1963); G. W. Gribble, J. M. Jasinski, and J. T. Pellicone, *Synthesis*, 766 (1978).

(17) Prepared from *p*-aminoacetophenone and acetic anhydride in acetic acid at 100 °C; mp 170–172 °C.

extracted with ethyl ether. The water layer was acidified and extracted into ethyl acetate three times. Drying and concentration gave 21.4 g (92%) of white solid **7**: mp 196–198 °C (lit.[18] mp 197–198 °C); IR (KBr) 1740, 1670 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 10.2 (s, 1 H, OH), 7.75 (d, $J$ = 9 Hz, 2 H, Ar), 7.6 (d, $J$ = 9 Hz, 2 H, Ar), 6.05 (s, 1 H, NH), 2.05 (s, 3 H, $CH_3$). Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.35; N, 6.76. Found: C, 57.86; H, 4.41; N, 6.76.

**4-Amino-α-oxophenylacetic Acid (8).** To 5.0 g (24 mmol) of **7** was added 50 mL of 6 N HCl and the mixture heated (steam bath) until all the solids had dissolved. The mixture was cooled and taken to pH 1.5 with 50% NaOH. Filtration gave 4.0 g (100%) of **8**: mp 90–200 °C (slow decomposition); IR (KBr) 3450, 2600, 1680, 1590 $cm^{-1}$; NMR (acetone-$d_6$) $\delta$ 7.8 (d, $J$ = 8 Hz, 2 H, Ar), 6.75 (d, $J$ = 8 Hz, 2 H, Ar), 5.0 (s, 3 H, $NH_2$ and OH). Anal. Calcd for $C_8H_7NO_3$: C, 58.18; H, 4.24; N, 8.48. Found: C, 58.39; H, 4.37; N, 8.11.

**Methyl 4-Amino-α-oxophenylacetate Dimethyl Ketal (9).** To 1.0 g (4.8 mmol) of **7** in 100 mL of methanol was added 4.5 mL of 98% $H_2SO_4$. After 48 h the mixture was concentrated to 20 mL, diluted with ethyl acetate, and extracted at 0 °C with saturated $NaHCO_3$. The organic layer was dried and concentrated to 0.92 g (85%) of a faint yellow solid, **9**: mp 89–91 °C; IR ($HCCl_3$) 1745, 1700, 1620 $cm^{-1}$; NMR ($DCCl_3$) $\delta$ 7.4 (d, $J$ = 9 Hz, 2 H, Ar), 6.7 (d, $J$ = 9 Hz, 2 H, Ar), 4.1 (s, 2 H, $NH_2$), 3.7 (s, 3 H, $CO_2CH_3$), 3.25 (s, 6 H, $OCH_3$). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.67; H, 6.67; N, 6.22. Found: C, 58.78; H, 6.57; N, 6.36.

**Acylation of 9. General Procedure.** A solution of **9** (2.0–12 mmol) in methylene chloride ($H_2CCl_2$) and 1.0 equiv of triethylamine was added to 1.0 equiv of the acid chloride in $H_2CCl_2$ at −20 °C. After complete addition (45 min), the mixture was taken to −5 °C for 3 h. It was then extracted with saturated $NaHCO_3$, dried, and concentrated to the ketal, which could be directly treated with acetonitrile, water, and 70% perchloric acid (10:1:0.5) to give the α-keto ester after workup as above. By use of the general procedure, 0.16 g (2.0 mmol) of acetyl chloride was converted to 0.39 g (88%) of methyl 4-acetamido-α-oxophenylacetate (**11a**), which was identical with an authentic sample.

**(*Z*)-4-Acetamido-α-(hydroxyimino)phenylacetic Acid (12).** To 5.00 g (24.2 mmol) of **7** in 60 mL of water was added 0.97 g (1.0 equiv) of NaOH. At 3 °C, 1.67 g (1.0 equiv) of $NH_2OH$·HCl, neutralized with 2.0 g (1.0 equiv) of $NaHCO_3$ in 50 mL of water, was added. The mixture was brought to room temperature and the pH maintained at 5.7 with $NaHCO_3$ as needed. After 4–6 h the pH remained constant. The mixture was acidified to pH 2.0 and extracted with ethyl acetate, which was dried and concentrated to a yellow solid. Recrystallization from dioxane–heptane gave 4.93 g (92%) of (*Z*)-**12**: mp 155–156 °C; IR (KBr) 3520, 2920, 2860, 1700 1635 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 10.1 (s, 1 H, NH), 7.65 (d, $J$ = 8 Hz, 2 H, Ar), 7.42 (d, $J$ = 8 Hz, 2 H, Ar), 2.08 (s, 3 H, $CH_3$). Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.50; N, 12.61. Found: C, 54.05; H, 4.54; N, 12.48.

**Methyl 4-Acetamido-α-oxophenylacetate (11a).** To 2.07 g (10.0 mmol) of **7** in 50 mL of $H_2CCl_2$ and 1.39 mL (1.0 equiv) of triethylamine was added, at 20 °C, 0.77 mL of methyl chloroformate (1.0 equiv). When evolution of $CO_2$ had ceased, the mixture was extracted at pH 7.5, dried, and concentrated to 2.11 g (95%) of a white solid, **11a**: mp 138–140 °C; IR (KBr) 3370, 1735, 1660 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 10.3 (s, 1 H, NH), 7.9 (d, $J$ = 9 Hz, 2 H, Ar), 7.75 (d, $J$ = 9 Hz, 2 H, Ar), 3.9 (s, 3 H, $OCH_3$), 2.15 (s, 3 H, $CH_3$). Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 4.98; N, 6.33. Found: C, 59.74; H, 5.11; N, 6.48.

**(*Z*)-Methyl 4-Acetamido-α-(methoxyimino)phenylacetate (13).** To 500 mg (2.25 mmol) of (*Z*)-**12** in methanol was added etheral diazomethane until the solution was permanently yellow. After 24 h, the mixture was diluted with ethyl acetate, extracted with saturated $NaHCO_3$, dried, and concentrated to 519 mg (92%) of (*Z*)-**13**: mp 93–95 °C; IR ($HCCl_3$) 1745, 1700 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 10.18 (s, 1 H, NH), 7.7 (d, $J$ = 9 Hz, 2 H, Ar), 7.4 (d, $J$ = 9 Hz, 2 H, Ar), 3.9 (s, 3 H, $OCH_3$), 3.87 (s, 3 H, $OCH_3$), 2.05 (s, 3 H, $CH_3$).

**(*Z*)- and (*E*)-Methyl 4-Acetamido-α-(methoxyimino)phenylacetate and the Free Acids (*Z*)-14 and (*E*)-16.** To 1.16 g (5.24 mmol) of **11a** in 10 mL of methanol was added 1.08 g (2.5 equiv) of $CH_3ONH_2$·HCl with 1.06 mL (2.5 equiv) of pyridine. After 5 h at reflux, the mixture was diluted with ethyl acetate, extracted with 2% HCl, dried, and concentrated to 1.31 g (100%) of a waxy solid, which was shown by high-pressure LC to be a 70:30 mixture of isomers. The entire mixture was treated with 0.81 mL (0.30 equiv) of 2 N NaOH in 5 mL of methanol for 30 min. Dilution with ethyl acetate and extraction at pH 9.5 followed by acidification to pH 2.0 gave an oil, which was taken up in ethyl acetate, dried, and concentrated to yield 345 mg (93% of expected *E* isomer) of (*E*)-**16**: mp 130–132 °C; IR (KBr) 3320, 1700, 1680 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 10.20 (s, 1 H, NH), 7.70 (d, $J$ = 9 Hz, 2 H, Ar), 7.45 (d, $J$ = 9 Hz, 2 H, Ar), 3.98 (s, 3 H, $OCH_3$), 2.10 (s, 3 H, $CH_3$). Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.08; N, 11.86. Found: C, 56.05; H, 5.30; N, 11.71. The ethyl acetate (that was base extracted) was concentrated and the residue treated with 1.89 mL (0.70 equiv) of 2 N NaOH. Workup as above yielded 805 mg (92% expected *Z* isomer) of (*Z*)-**14**, identical in all respects with the material prepared similarly from **13**: mp 164–165 °C; IR (KBr) 3300, 1710, 1625, 1605 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 10.18 (s, 1 H, NH), 7.69 (d, $J$ = 9 H, 2 H, Ar), 7.45 (d, $J$ = 9 Hz, 2 H, Ar), 3.90 (s, 3 H, $OCH_3$), 2.10 (s, 3 H, $CH_3$). Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.08; N, 11.86. Found: C, 55.91; H, 5.00; N, 11.72.

**(*Z*)-4-Acetamido-α-(methoxyimino)phenylacetic Acid Imidazolide (17).** To 236 mg (1.00 mmol) of **14** in 5 mL of DMF was added 162 mg (1.0 equiv) of 1,1′-carbonyldiimidazole. After 24 h, the mixture was diluted with ethyl acetate, extracted with water three times, dried, and concentrated to 279 mg (97%) of a yellow oil: IR (neat) 3230, 1730, 1685, 1600 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 10.25 (s, 1 H, NH), 8.3 (s, 1 H, CH), 7.6 (m, 5 H, Ar and CH), 7.2 (s, 1 H, CH), 3.95 (s, 3 H, $OCH_3$), 2.10 (s, 3 H, $CH_3$).

**(*Z*)-4-Acetamido-α-(methoxyimino)-*N*-phenylbenzeneacetamide (18).** To 100 mg (0.350 mmol) of the imidazolide **17** was added 2 mL of DMF and 1.0 mL of aniline (11 mmol). After 18 h at room temperature, only a small amount of product was formed, and the mixture was heated to 80 °C for 16 h. It was diluted with ethyl acetate, extracted with 1% HCl, dried, and concentrated to 108 mg (100%) of **18**: mp 109–111 °C; IR (KBr) 3270, 1660, 1600 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 10.7 (s, 1 H, NH), 10.2 (s, 1 H, NH), 7.5 (m, 9 H, Ar), 3.95 (s, 3 H, $OCH_3$), 2.1 (s, 3 H, $CH_3$). Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.59; H, 5.47; N, 13.50. Found: C, 65.28; H, 5.44; N, 13.38.

**4-[[(Benzyloxy)carbonyl]amino]-α-oxophenylacetic Acid (19).** To 10 mL (2.0 equiv) of benzyl chloroformate in 5 mL of dry tetrahydrofuran (THF) at −10 °C was added a solution of 4.00 g (29.6 mmol) of 4-aminoacetophenone (**5**) and 4.0 mL (1.0 equiv) of triethylamine in 20 mL of THF. After 1 h at −10 °C, the mixture was stirred at 25 °C for 5 h. It was diluted with ether, filtered, extracted with 2% HCl, dried, and concentrated. The residue crystallized from $H_2CCl_2$–pentane to give 4.35 g (55%) of 4-[[(benzyloxy)carbonyl]amino]acetophenone: mp 130–132 °C; IR (Nujol) 3300, 1725, 1670, 1595 $cm^{-1}$; NMR ($DCCl_3$) $\delta$ 7.8 (d, $J$ = 8 Hz, 2 H, Ar), 7.4 (d, $J$ = 8 Hz, 2 H, Ar), 7.25 (s, 5 H, Ar), 7.1 (s, 1 H, NH), 5.1 (s, 2 H, $CH_2$), 2.5 (s, 3 H, $CH_3$). This material was oxidized with selenium dixodie as described for the preparation **7**. Thus 25.0 g (92.9 mmol) of 4-[[(benzyloxy)carbonyl]amino]acetophenone gave 20.8 g (75%) of **19**: mp 114–115 °C; IR (KBr) 1735, 1720, 1670 $cm^{-1}$; NMR (acetone-$d_6$, $D_2O$) $\delta$ 8.05 (d, $J$ = 9 Hz, 2 H, Ar), 7.8 (d, $J$ = 9 Hz, 2 H, Ar), 7.4 (s, 5 H, Ar), 5.25 (s, 2 H, $CH_2$). Anal. Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.35; N, 4.68. Found: C, 64.22; H, 4.37; N, 4.61.

**4-[[(Benzyloxy)carbonyl]amino]-α-(hydroxyimino)-phenylacetic Acid (20).** By use of the procedure used for the preparation of **12**, 7.2 g (24 mmol) of **19** was converted to 6.5 g (87%) of **20**: mp 143–145 °C; IR (KBr) 1710, 1600 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 12.5 (s, 2 H, 2 OH), 10.05 (s, 1 H, NH), 7.5 (m, 9 H, Ar), 5.25 (s, 2 H, $CH_2$). Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.15; H, 4.46; N, 8.92. Found: C, 61.00; H, 4.70; N, 9.06.

**(*Z*)-Methyl 4-[[(Benzyloxy)carbonyl]amino]-α-(methoxyimino)phenylacetate (21).** Following the procedure for the preparation of **13**, 2.30 g (10.7 mmol) of **20** was converted to 2.39 g (90%) of **21**: mp 96–98 °C; IR ($HCCl_3$) 3340, 1740, 1610 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 10.2 (s, 1 H, NH), 7.5 (m, 9 H, Ar), 5.2 (s, 2 H, $CH_2$), 3.95 (s, 3 H, $OCH_3$), 3.9 (s, 3 H, $OCH_3$).

(18) F. Krohnke, *Chem. Ber.*, **80**, 298 (1947).

**(*Z*)-Methyl 4-(Methoxyimino)phenylacetate (22).** To 2.00 g of 10% palladium on carbon (Ventron) and 3.42 g (10.0 mmol) of **21** was added 50 mL of ethyl acetate and 20 mL of cyclohexene. The mixture was taken to 50 °C for 3 h, filtered, and concentrated to 20.6 g (99%) of a faint yellow solid, **22**: mp 79–80 °C; IR ($CCl_4$) 3500, 3420, 1750, 1630 $cm^{-1}$; NMR ($DCCl_3$) δ 7.3 (d, $J$ = 8 Hz, 2 H, Ar), 6.6 (d, $J$ = 8 Hz, 2 H, Ar), 3.9 (s, 3 H, $OCH_3$), 3.85 (m, 5 H, $OCH_3$ and $NH_2$). Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.63; H, 5.77; N, 13.46. Found: C, 57.32; H, 5.71; N, 13.24. This material (103 mg, 0.50 mmol) was treated with acetyl chloride (1.0 equiv) and triethylamine (1.0 equiv) at −10 °C in $H_2CCl_2$ to give 125 mg (99%) of (*Z*)-**13**, identical in all respects with authentic material.

**(*Z*)-4-[[(Benzyloxy)carbonyl]amino]-α-[[(tetrahydro-2*H*-pyran-2-yl)oxy]imino]phenylacetic Acid (23).** To 2.50 g (7.96 mmol) of (*Z*)-**20** in 15 mL of dioxane were added 1.10 mL (1.5 equiv) of dihydropyran and 50.0 mg (0.25 mmol) of *p*-toluenesulfonic acid. After 16 h, the mixture was diluted with ethyl acetate and extracted twice with water. Purification by column chromatography gave 2.15 g (68%) of a white solid, (*Z*)-**23**: mp 134–135 °C; IR (KBr) 1745, 1715, 1610, 1225 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) δ 14.0 (br s, 1 H, $CO_2H$), 10.0 (s, 1 H, NH), 7.45 (m, 9 H, Ar), 5.35 (s, 1 H, CH), 5.2 (s, 2 H, $CH_2$), 3.7 (m, 2 H, $OCH_2$), 1.7 (m, 6 H, alkyl). Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.32; H, 5.53; N, 7.04. Found: C, 63.03; H, 5.80; N, 6.97. Alternatively **23** could be prepared from the keto acid **19** with (tetrahydropyran-2-yl)hydroxylamine[14] (1.2 equiv) in pyridine at 0 °C for 4 h. (*Z*)-**23** was obtained in 59% yield and 95% stereospecificity.

**(*Z*)-Methyl 4-Amino-α-[[(tetrahydro-2*H*-pyran-2-yl)oxy]imino]phenylacetate (25).** To 15.0 g (37.7 mmol) of **23** in 250 mL of methanol was added, at 0 °C, an excess of ethereal diazomethane. The mixture was diluted with ether, extracted with saturated $NaHCO_3$, dried, and concentrated to 15.2 g (98%) of **24**: mp 114–115 °C; IR (KBr) 3300, 1740 $cm^{-1}$; NMR ($DCCl_3$) δ 7.4 (m, 9 H, Ar), 7.1 (s, 1 H, NH), 5.4 (br s, 1 H, CH), 5.15 (s, 2 H, $CH_2$), 3.9 (s, 3 H, $OCH_3$), 3.8 (m, 2 H, $OCH_2$), 1.6 (m, 6 H, alkyl). To 11.7 g (28.3 mmol) of this material in 250 mL of ethyl acetate and 5.00 g of 10% palladium on carbon was added a stream of $H_2$ for 30 min. The mixture was filtered and concentrated to 7.87 g (100%) of an oil, (*Z*)-**25**: IR ($CHCl_3$) 3420, 1745, 1630 $cm^{-1}$; NMR ($DCCl_3$) δ 7.3 (d, $J$ = 9 Hz, 2 H, Ar), 6.55 (d, $J$ = 9 Hz, 2 H, Ar), 5.4 (br s, 1 H, CH), 3.9 (s, 3 H, $OCH_3$), 3.7 (m, 4 H, $OCH_2$ and $NH_2$), 1.65 (m, 6 H, alkyl). This amine was stored at −40 °C.

**Acylation and Hydrolysis of 25. General Procedure.** To 1 equiv of the acid chloride (or anhydride) in $H_2CCl_2$ at 0 °C was added a 1:1 mixture of **25** and triethylamine over several minutes. After 30 min, the mixture was extracted with saturated $NaHCO_3$, dried, and concentrated to the ester, **26**. The acylated amine **26** was then dissolved in pyridine at 90–100 °C and treated with 4 equiv of lithium iodide (Ventron). After 4 h, the mixture was diluted with ethyl acetate, extracted with 2% HCl and saturated $NaHSO_3$, dried, and concentrated to give the acid **27**.

**(a) With Furoyl Chloride.** By use of the general procedure, 0.62 mL (6.0 mmol) of furoyl chloride was converted with **25** to 1.38 g of **26a**, obtained as a white solid after trituration with ethyl acetate and hexane: mp 162–164 °C; IR (KBr) 3350, 1730, 1670, 1230 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) δ 10.4 (s, 1 H, NH), 7.8 (m, 3 H, Ar), 7.5 (m, 3 H, Ar), 6.7 (m, 1 H, Ar), 5.4 (s, 1 H, CH), 3.9 (s, 3 H, $OCH_3$), 3.7 (m, 2 H, $OCH_2$), 1.65 (m, 6 H, alkyl). Hydrolysis of 744 mg (2.00 mmol) of **26a** gave 620 mg of the acid **27a**: mp 126–127 °C; IR (KBr) 3320, 1740, 1670, 1630 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) δ 10.4 (s, 1 H, NH), 7.7 (m, 6 H, Ar), 6.7 (m, 1 H, Ar), 5.4 (s, 1 H, $OCH_2$), 3.7 (m, 2 H, $OCH_2$), 1.7 (m, 6 H, alkyl).

**(b) With Benzoyl Chloride.** By use of the general procedure, 0.14 mL (1.0 mmol) of benzoyl chloride was converted with **25** to 325 mg of **26b**, obtained as a white solid after crystallization from $H_2CCl_2$ and pentane: mp 170–172 °C; IR (KBr) 3380, 1750, 1680 $cm^{-1}$; NMR ($DCCl_3$) δ 8.3 (s, 1 H, NH), 7.6 (m, 9 H, Ar), 5.45 (s, 1 H, CH), 3.95 (s, 3 H, $OCH_3$), 3.8 (m, 2 H, $OCH_2$), 1.75 (m, 6 H, alkyl). Hydrolysis of 382 mg (1.00 mmol) of **26b** gave 325 mg of **27b** as a white solid: mp 139–141 °C; IR (KBr) 3360, 1740, 1660 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) δ 10.5 (s, 1 H, NH), 8.0 (m, 4 H, Ar), 7.55 (m, 5 H, Ar), 5.4 (m, 1 H, CH), 3.7 (m, 2 H, $OCH_2$), 1.7 (m, 6 H, alkyl).

**(c) With *O*-Acetylmandeloyl Chloride.** By use of the general procedure, 1.2 mL (5.0 mmol) of the acid chloride was converted with **25** to 1.15 g of **26c** which was obtained as a yellow oil: IR ($HCCl_3$) 3440, 1745, 1710 $cm^{-1}$; NMR ($DCCl_3$) δ 8.25 (s, 1 H, NH), 7.5 (m, 9 H, Ar), 6.2 (s, 1 H, PhCH), 5.5 (s, 1 H, CH), 4.0 (s, 3 H, $OCH_3$), 3.8 (m, 2 H, $OCH_2$), 2.3 (s, 3 H, $CH_3$), 1.7 (m, 6 H, alkyl). Hydrolysis of 1.0 g (2.3 mmol) of **26c** gave 0.89 g of the acid **27c** as a glass: IR (KBr) 3460, 1740, 1695 $cm^{-1}$; NMR ($DCCl_3$) δ 8.6 (s, 1 H, NH), 7.45 (m, 7 H, Ar), 6.8 (m, 2 H, Ar), 6.15 (s, 1 H, PhCH), 5.45 (s, 1 H, CH), 3.8 (m, 2 H, $OCH_2$), 2.2 (s, 3 H, $CH_3$), 1.7 (m, 6 H, alkyl).

**(d) With Trifluoroacetic Anhydride.** By use of the general procedure, 630 mg (3.00 mmol) of trifluoroacetic anhydride was converted with **25** to 930 mg of **26d**, which was directly hydrolyzed to give 608 mg of the acid **27d** as a glass: IR (KBr) 3280, 1720, 1605 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) δ 11.5 (s, 1 H, NH), 7.9 (d, $J$ = 9 Hz, 2 H, Ar), 7.65 (d, $J$ = 9 Hz, 2 H, Ar), 5.4 (m, 1 H, CH), 3.7 (m, 2 H, $OCH_2$), 1.65 (m, 6 H, alkyl).

**(e) With Benzyl (−)-(*R*)-4-Chloro-4-oxo-2-[[(benzyloxy)carbonyl]amino]butyrate.**[19] By use of the general procedure, 787 mg (2.00 mmol) of the acid chloride was converted with **25** to 1.01 g of **26e**, obtained as a glass: IR (KBr) 3350, 1745–1710 $cm^{-1}$; NMR ($DCCl_3$) δ 7.9 (s, 1 H, NH), 7.5 and 7.3 (m, 14 H, Ar), 6.05 (d, $J$ = 7 Hz, 1 H, CHN**H**), 5.45 (m, 1 H, OCH), 5.15 and 5.10 (2 s, 4 H, 2 $CH_2$), 4.7 (m, 1 H, CH), 3.9 (s, 3 H, $OCH_3$), 3.8 (m, 2 H, $OCH_2$), 2.95 (d, $J$ = 6 Hz, 2 H, CHC**H**$_2$), 1.7 (m, 6 H, alkyl). This material could not be hydrolyzed by the general procedure.

**Methyl 4-(Benzylamino)-α-oxophenylacetate Dimethyl Ketal (30a).** To 1.57 g (7.00 mmol, 1.4 equiv) of **9** in 12 mL of ethanol and 0.12 mL (0.40 equiv) of acetic acid was added 5.28 g (4.98 mmol) of benzaldehyde. After 15 min 0.19 g (1.8 equiv) of sodium cyanoborohydride was added and the mixture stirred for 30 min. It was diluted with ethyl acetate, extracted with water, dried, and concentrated. The residue was purified by column chromatography (ether–benzene–hexane, 2:3:2) to give 1.59 g (72%) of **30a** as a white solid: mp 149–152 °C; IR (KBr) 3360, 1750, 1680 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) δ 7.25 (m, 7 H, Ar), 6.5 (m, 3 H, PhNH and Ar), 4.25 (d, $J$ = 8 Hz, 2 H NHC**H**$_2$), 3.6 (s, 3 H, $CO_2CH_3$), 3.1 (s, 6 H, $OCH_3$). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.49; H, 6.67; N, 4.44. Found: C, 68.20; H, 6.80; N, 4.54.

**Methyl 4-[[4-Oxo-4-(benzyloxy)-3-[[(benzyloxy)carbonyl]amino]butyl]amino]-α-oxophenylacetate Dimethyl Ketal (30b).** By use of the identical procedure employed for **30a**, 1.36 g (3.98 mmol) of benzyl 4-oxo-2-[[(benzyloxy)carbonyl]amino]butanoate[20] was converted to 1.54 g (72%) of **30b**, obtained as an oil: IR ($HCCl_3$) 3440, 1740, 1610 $cm^{-1}$; NMR ($DCCl_3$) δ 7.35 (m, 12 H, Ar), 6.5 (d, $J$ = 9 Hz, 2 H, Ar), 5.5 (d, $J$ = 7 Hz, 1 H, CHN**H**), 5.2 (s, 4 H, 2 $OCH_2$), 4.6 (m, 1 H, CH), 3.7 (s, 3 H, $CO_2CH_3$), 3.3 (s, 6 H, $OCH_3$), 3.0 (m, 1 H, $CH_2$N**H**), 2.1 (m, 2 H, NHC**H**$_2$), 1.3 (m, 2 H, NHCH$_2$C**H**$_2$).

**4-(Benzylamino)-α-oxophenylacetic Acid (31).** To 315 mg (1.00 mmol) of **30a** was added 2 mL of pyridine and 500 mg (4 equiv) of lithium iodide. After 5 h at 90 °C, the mixture was diluted with ethyl acetate and extracted with water at pH 9.0. The water layer was acidified to pH 2.0 and extracted with ethyl acetate, which was dried and concentrated to 254 mg (100%) of **31**, obtained as a yellow powder: mp >300 °C; IR (KBr) 3400, 1750, 1745, 1570 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) δ 7.6 (m, 3 H, Ar and NH), 7.3 (s, 5 H, Ar), 6.65 (d, $J$ = 9 Hz, 2 H, Ar), 4.4 (d, $J$ = 4 Hz, 2 H, $CH_2$).

**4-(Benzylamino)-α-(hydroxyimino)phenylacetic Acid (32).** To 255 mg (1.00 mmol) of the keto acid **31** in 2 mL of water and 0.5 mL of 2 N sodium hydroxide was added 139 mg (2.1 equiv) of hydroxylamine hydrochloride neutralized with 168 mg of $NaHCO_3$. The mixture was heated to 60 °C for 6 h at pH 6.4. The pH was then adjusted to 2.0, and the mixture extracted into ethyl acetate, dried, and concentrated to give 260 mg (96%) of **32** as a faint yellow solid: mp 134–135 °C; IR (KBr) 3400, 1725, 1605 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) δ 11.1 (s, 1 H, NOH), 7.3 (m, 8 H,

(19) M. Bergman, L. Zervas, and L. Salzmann, *Chem. Ber.*, **66**, 1288 (1933); M. Bergman and L. Zervas, *ibid.*, **65**, 1192 (1932).

(20) The aldehyde was prepared from 2-aminobutyrolactone hydrobromide in four steps. The amino group was protected with benzylchloroformate in water–acetone, followed by hydrolysis with sodium hydroxide in dioxane to sodium 2-[[(benzyloxy)carbonyl]amino]-4-hydroxybutanoate. This salt was esterified with benzyl bromide, and the alcohol was oxidized with pyridine–chromium trioxide in dichloromethane to the aldehyde in 51% overall yield.

Ar and NH), 6.6 (d, $J$ = 9 Hz, 2 H, Ar), 4.3 (m, 2 H, $CH_2$). Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.71; H, 5.19; N, 10.37. Found: C, 67.09; H, 5.37; N, 10.51.

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**Registry No.** **5**, 99-92-3; **6**, 2719-21-3; **7**, 73549-48-1; **7** (*E*-oxime derivative), 75626-40-3; **8**, 15535-99-6; **9**, 75626-41-4; **11a**, 75626-42-5; **11a** (*E*-oxime derivative), 75626-43-6; **11a** (*Z*-oxime derivative), 75626-44-7; **12**, 75626-45-8; **13**, 75626-46-9; **14**, 75626-47-0; **16**, 75626-48-1; **17**, 75626-49-2; **18**, 75626-50-5; **19**, 75626-51-6; **19** (*E*-oxime derivative), 75626-52-7; **19** methyl ester (*E*-oxime derivative), 75626-53-8; **19** methyl ester (*Z*-oxime derivative), 75626-54-9; **20**, 75626-55-0; **21**, 75626-56-1; **22**, 75626-57-2; **23**, 75626-58-3; **24**, 75626-59-4; **25**, 75626-60-7; **26a**, 75626-61-8; **26b**, 75626-62-9; **26c**, 75640-91-4; **26d**, 75626-63-0; **26e**, 75626-64-1; **27a**, 75626-65-2; **27b**, 75626-66-3; **27c**, 75626-67-4; **27d**, 75626-68-5; **30a**, 75626-69-6; **30b**, 75626-70-9; **31**, 75626-71-0; **32**, 75626-72-1; 1,1'-carbonyldiimidazole, 530-62-1; aniline, 62-53-3; 4-[[(benzyloxy)carbonyl]amino]acetophenone, 72531-10-3; dihydropyran, 110-87-2; (tetrahydropyran-2-yl)hydroxylamine, 6723-30-4; furoyl chloride, 527-69-5; benzoyl chloride, 98-88-4; *O*-acetylmandeloyl chloride, 1638-63-7; trifluoroacetic anhydride, 407-25-0; benzyl (-)-(*R*)-4-chloro-4-oxo-2-[[(benzyloxy)carbonyl]amino]butyrate, 75626-73-2; benzaldehyde, 100-52-7; benzyl 4-oxo-2-[[(benzyloxy)carbonyl]amino]butanoate, 75626-74-3; 2-aminobutyrolactone hydrobromide, 6305-38-0; sodium 2-(benzyloxy)carbonyl]amino]-4-hydroxybutanoate, 75626-75-4.

# Transannular Reactions of Dibenzo[*a*,*d*]cycloalkenes. 3.[1] Nature of the Amine to Olefin Ring Closure

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An efficient, regiospecific, intramolecular amine to olefin addition is described. Evidence is presented which suggests that the reaction pathway has radical character and involves nitrogen participation. Factors considered are the structure of the substrate, the initiating base, the effect of reagent addition order, sensitivity to oxygen and other radical inhibitors, the ESR signature, and the fate of hydrogen at key reaction centers as determined by deuterium labeling.

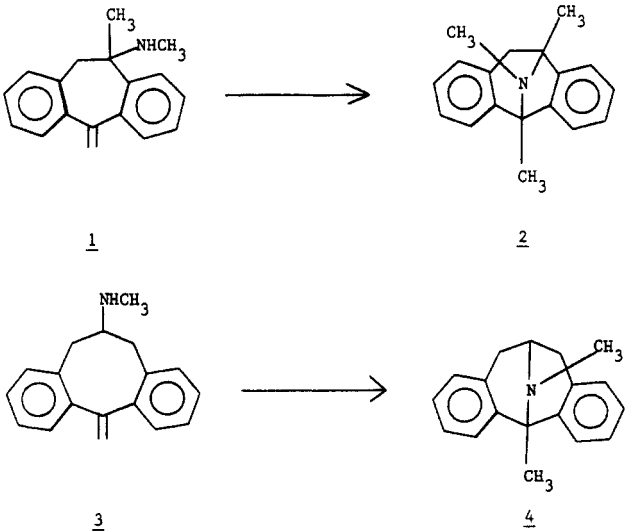
The direct addition of amines to simple olefins is an infrequently utilized synthetic reaction. In those cases where addition is observed, conditions sufficently basic for formation of the amide anion,[2] elevated temperatures, and protracted reaction times are required.[4] These conditions usually produce low yields of product mixtures.

In the course of synthetic studies on bridged ring cyclic imines,[1,6] we observed a regiospecific amine to olefin addition which took place rapidly at room temperature in excellent yield. The characteristics of this reaction indicated it was not a nucleophilic addition, and we, therefore, undertook a closer study of its mechanism. Reported here are the results of that study.

## Results

Our earlier work on bridged ring cyclic imines[1] revealed that the amino olefins 1 and 3 could be converted in high yield to the cyclic structures 2 and 4, respectively. Addition of 0.2 equiv of butyllithium to a stirred THF solution of 1 or 3 maintained under nitrogen at room temperature rapidly gave 2 or 4, respectively. The mechanism initially considered (Scheme I) involved formation of the amide anion 5 followed by intramolecular nucleophilic addition to the olefin. However, this formulation proved inadequate to explain all of the characteristics of the reaction. For example, successful reactions were always accompanied by a persistent deep bronze color. Exposure of the reaction mixture to air caused the bronze color to fade and the reaction to stop.

In THF dried over molecular sieves, the amount of butyllithium required varied considerably (0.5–1.2 equiv) from run to run. If this solvent was distilled from ben-




(1) B. E. Evans, P. S. Anderson, M. E. Christy, C. D. Colton, D. C. Remy, K. E. Rittle, and E. L. Engelhardt, *J. Org. Chem.*, **44**, 3127 (1979).

(2) March[3] describes the addition of amines to olefins as "...nearly always nucleophilic", noting that "...basic catalysts are sometimes used, so that $RN^-H$ or $R_2N^-$ is the actual nucleophile".

(3) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", 2nd ed., McGraw-Hill, New York, 1977, pp 704–705.

(4) A recent statement of the generally held view is provided by Barton and Ollis:[5] "Nucleophilic addition of ammonia and amines to simple alkenes is difficult but is possible with catalysts at high temperatures and pressures".

(5) D. H. R. Barton and W. D. Ollis, "Comprehensive Organic Chemistry: The Synthesis and Reactions of Organic Compounds", Vol. 2, Pergamon Press, New York, 1979, p 11.

(6) (a) D. C. Remy, P. S. Anderson, M. E. Christy, and B. E. Evans, *J. Org. Chem.*, **43**, 4311 (1978); (b) M. E. Christy, P. S. Anderson, S. F. Britcher, C. D. Colton, B. E. Evans, D. C. Remy, and E. L. Engelhardt, *ibid.*, **44**, 3117 (1979).

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