(11) A. Schweig, U. Weidner, R. K. Hill, and D. A. Cullison, *J. Amer. Chem. Soc.*, **95**, 5427 (1973).
(12) P. Kovacic and C. Wu, *J. Org. Chem.*, **26**, 759 (1961).
(13) V. Boekelheide and R. A. Hollins, *J. Amer. Chem. Soc.*, **92**, 2352 (1970). We are grateful to Professor Boekelheide for generously providing us with the triene.
(14) V. Boekelheide, I. D. Reingold, and M. Tuttle, *J. Chem. Soc., Chem. Commun.*, 406 (1973).
(15) N. L. Allinger, B. J. Gorden, S.-E. Hu, and R. A. Ford, *J. Org. Chem.*, **32**, 2272 (1967).

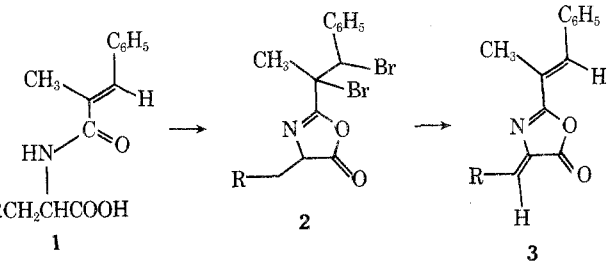
Stereoselective Formation of a Pseudo Oxazolone

Edward G. Breitholle and Charles H. Stammer*

Department of Chemistry, University of Georgia, Athens, Georgia 30602

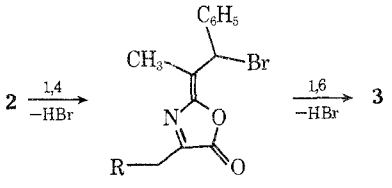
Received December 18, 1973

It has recently been shown in our laboratories that unsaturated azlactones (**3**) can be prepared by treatment of *N*-cinnamoyl amino acids (**1**) with a pyridine perbromide–acetic anhydride–pyridine mixture.[1] This reaction most



1 **2** **3**

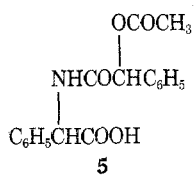
likely proceeds through a dibromo saturated azlactone (**2**), since we have shown[1] that dibromodihydrocinnamoyl amino acids also afford **3** under these reaction conditions. The halogenated intermediate, **2**, apparently undergoes a 1,4-dehydrobromination, giving a pseudo oxazolone, **4**, which again dehydrobrominates giving **3**. It was shown



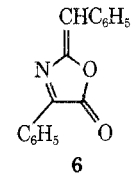
4

that the configuration of the 1-methylstyryl group was unchanged during the **1** → **3** conversion. If we assume trans bromination to give **2**, then knowledge of the steric course of the 1,4-dehydrobromination step would allow us to infer the stereochemistry of the 1,6-dehydrobromination and, consequently, the configuration of the new double bond at the 4 position. We chose to examine the stereochemistry of the 1,4 elimination by using the two diastereomers of an *N*-mandeloylphenylglycine derivative (**5**), since the required chiral starting materials are readily available. If the reaction occurs stereospecifically, the DD,LL racemate should afford one stereoisomer of the pseudo oxazolone, **6**, while its diastereomer, the DL,LD isomer, should give the other geometric isomer. Formation of the same isomer of **6** from both diastereomers of **5** would indicate that the reaction is stereoselective.

Racemic mandelic acid was O-acetylated and coupled to racemic phenylglycine to give the mandeloyl derivative **5**, which consisted of a diastereomeric mixture. When **5** was treated with an acetic anhydride–pyridine mixture the crystalline pseudo oxazolone **6** was formed. Recrystallization of crude **6** gave the pure compound having physical properties in agreement with those previously reported by Adembri.[2] Liquid chromatography of crude **6** failed to show the presence of a second oxazolone and ^{13}C nmr spectroscopy showed clearly that only one stereoisomer was present. This indicated strongly that the reaction was stereoselective, giving only the more stable product.

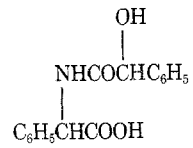


5



6

In order to check this result, the optically active mandeloylphenylglycines (**5**) were prepared. *N*-(*O*-Acetyl-D(−)-mandeloyl)-D-(−)-phenylglycine[3] and *N*-(*O*-acetyl-D(−)-mandeloyl)-L(+)-phenylglycine were prepared by the same method used to prepare the racemate. When these isomers were subjected to the acetic anhydride–pyridine treatment, the pseudo oxazolone obtained was identical in all respects with that obtained from the racemate. We were concerned that the results of these experiments might be invalidated by the possibility of racemization of the mandelic acid chiral center during the Schotten–Baumann coupling of the acid chloride with phenylglycine. In order to check this, *N*-(*O*-acetyl)-D(−)-mandelic acid was coupled with each of the enantiomers of phenylglycine methyl ester using carbodiimide, and the ester functions were saponified to give both diastereomers of *N*-mandeloylphenylglycine (**7**). The acetic anhydride–pyridine reagent converted these two compounds into the same pseudo oxazolone **6** in yields almost identical with those obtained before.



7

We can conclude from these results that the 1,4 dehydrobromination of intermediate **2** is stereoselective rather than stereospecific. This means that the overall conversion of **1** → **3** is most probably stereoselective. In the six cases that we have investigated[1] so far, the *Z* isomer is formed predominantly when R is aliphatic and exclusively when R is aromatic.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer as Nujol mulls with polystyrene as a standard. The proton nuclear magnetic resonance spectra were recorded on a Varian HA-100 spectrometer with tetramethylsilane as the internal or external standard. All chemical shifts are reported in parts per million. The carbon-13 nuclear magnetic resonance spectrum was determined on a JEOL PFT-100 spectrometer. The ultraviolet-visible spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer. Melting points were uncorrected and determined on a Nagle Model Y6 hot stage. Elemental analyses were carried out by Atlantic Microlabs, Atlanta, Ga. Observed rotations were obtained on a Perkin-Elmer Model 141 polarimeter.

***O*-Acetyl-L(+)-mandelic Acid.** A mixture of 7.2 g (0.0475 mol) of L(+)-mandelic acid, $[\alpha]^{27}D$ +158° (*c* 1.0, H_2O) [lit.[4] $[\alpha]^{26}D$ +157° (*c* 1.07, H_2O)], and 20 ml (0.278 mol) of acetyl chloride was warmed on a water bath for 2 hr. The excess acetyl chloride was removed *in vacuo*, leaving a colorless oil which crystallized after 2 days. Recrystallization from benzene–*n*-hexane gave 59 g (69%) of the acid: mp 95–97.5° (lit.[5] mp 96.8°); $[\alpha]^{27}D$ +148° (*c* 1.87, acetone) [lit.[6] $[\alpha]^{25}D$ +153° (*c* 2.0, acetone)]; nmr ($CDCl_3$) δ 2.10 (s, 3 H, CH_3), 5.95 (s, 1 H, C_6H_5CHO), 7.18–7.48 (m, 5 H, C_6H_5), 11.70 ppm (s, 1 H, COOH); ir (Nujol) 1745 (C=O ester), 1700 cm^{-1} (C=O acid).

O-Acetyl-D(−)-mandelic Acid. The method used was similar to that used for the L(+) isomer. Starting with 2.75 g (18 mmol) of D(−)-mandelic acid, $[\alpha]^{27}D$ −147° (*c* 1.67, 20% HCl) [lit.[4] $[\alpha]^{25}D$ −154° (*c* 2.06, H_2O)], and 8 ml of acetyl chloride, 2.77 g (79%), mp 80–81°, of the acid was obtained: $[\alpha]^{27}D$ −155° (*c* 1.34, acetone) [lit.[5] $[\alpha]^{20}D$ −157° (*c* 2.4, acetone)]; ir (Nujol) 1745 (C=O ester), 1695 cm^{-1} (C=O acid); nmr ($CDCl_3$) δ 2.10 (s, 3 H, CH_3COO), 6.00 (s, 1 H, -OCHCOOH), 7.23–7.60 (m, 5 H, C_6H_5), 11.50 ppm (s, 1 H, COOH).

N-[O-Acetyl-DL-mandeloyl]-DL-phenylglycine (5). To a solution of 31.24 g (0.20 mol) of phenylglycine and 210 ml of 1 *N* sodium hydroxide contained in a 500-ml, three-necked, round-bottomed flask equipped with two dropping funnels and a stirrer and cooled with an ice bath was added dropwise over a 1 hr period 40.47 g (0.193 mol) of *O*-acetyl-DL-mandeloyl chloride[7] and 260 ml of 1 *N* sodium hydroxide. After an additional 30 min of stirring, the mixture was acidified, the combined extracts were dried with anhydrous magnesium sulfate and filtered, and the filtrate was evaporated *in vacuo*, yielding 51.0 g (82%) of the crude product. Recrystallization from ethyl acetate–petroleum ether (bp 30–60°) (6:1) gave 42.6 g (69%) of the acid: mp 172–181°; ir (Nujol) 3375 (NH), 2475–2600 (COOH), 1745 (CH_3COO–), 1718 (COOH), 1625 cm^{-1} (CONH–); nmr (TFA) δ 2.25 (s, 3 H, CH_3), 5.7 (d, 1 H, C_6H_5CHNH), 6.35 (s, 1 H, C_6H_5CHO–), 7.28–7.50 (m, 10 H, 2 C_6H_5), 7.91 ppm (d, 1 H, NH).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.83; H, 5.27; N, 4.19.

N-[O-Acetyl-L(+)-mandeloyl]-D(−)-phenylglycine (5). This compound was prepared by condensation of 16.63 g (0.11 mol) of D(−)-phenylglycine with 25.5 g (0.12 mol) of *O*-acetyl-L(+)-mandeloyl chloride.[8] A 33.0-g (84%) yield of crude product was recrystallized from an ethyl acetate–petroleum ether mixture, giving 22.2 g (57%), mp 193–197°, of pure acid. The analytical sample was recrystallized from an acetic acid–H_2O mixture: mp 199–203°; $[\alpha]^{20}D$ −53.11° (*c* 3.82, HOAc); ir (Nujol) 3295 (NH), 2490 (COOH), 1720 (CH_3COO), 1600 cm^{-1} (CONH); nmr (TFA) δ 2.18 (s, 3 H, CH_3CO_2), 5.68 (d, 1 H, OCHNH), 6.30 (s, 1 H, OCHOAc), 7.20–7.49 (m, 10 H, 2 C_6H_5), 7.92 ppm (d, 1 H, NHCO).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05, H, 5.23; N, 4.28. Found: C, 66.02; H, 5.35; N, 4.28.

N-[O-Acetyl-D(−)-mandeloyl]-D(−)-phenylglycine (5). The procedure used was the same used in preparing the racemic **5** and the LD-**5**. A 67% yield, mp 188–198°, of the acid was obtained. The analytical sample was recrystallized from acetic acid–water: mp 202–205°; $[\alpha]^{21}D$ −62.0° (*c* 1.23, HOAc); ir (Nujol) 3300 (NH), 1748 (CH_3COO–), 1723 (COOH), 1660 cm^{-1} (-CONH–); nmr [$(CD_3)_2CO$] δ 2.09 (s, 3 H, CH_3), 5.55 (d, 1 H, C_6H_5CHNH–), 6.12 (s, 1 H, C_6H_5CHO), 7.18–7.58 (m, 10 H, 2 C_6H_5), 8.0 ppm (d, 1 H, NH).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.80; H, 5.30; N, 4.32.

N-[O-Acetyl-L (+)-mandeloyl]-D(−)-phenylglycine Methyl Ester. To a suspension of 2.09 g (10.4 mmol) of D(−)-phenylglycine methyl ester hydrochloride[9] in 30 ml of methylene chloride was added 1.45 (10.4 mmol) of triethylamine. After 25 min at room temperature 2.0 g (10.4 mmol) of *O*-acetyl-L(+)-mandelic acid was added followed by 2.18 g (10.6 mmol) of *N,N'*-dicyclohexylcarbodiimide (DCC). The light green solution was stirred at room temperature for 2 hr and cooled in an ice bath. Excess DCC was destroyed with trifluoroacetic acid, and the *N,N'*-dicyclohexylurea (2.1 g, 89%) was filtered. The filtrate was washed with 5% sodium bicarbonate and 0.5 *N* hydrochloric acid, dried with anhydrous sodium sulfate, clarified with Norit, and evaporated to dryness *in vacuo*, leaving a solid residue, 3.4 g. The crude product was recrystallized from methylene chloride–hexane, giving 2.38 g (67%), mp 154–157°, of the diester: $[\alpha]^{31}D$ − 24.8° (c 0.56, MeOH); ir (Nujol) 3315 (NH), 1750 ($COOCH_3$), 1725 (CH_3COO), 1695 cm^{-1} (-CONH–); nmr ($CDCl_3$) δ 2.05 (s, 3 H, CH_3COO), 3.55 (s, 3 H, $COOCH_3$), 5.4 (d, 1 H, -CHNH), 5.95 (s, 1 H, -CHOAc), 6.95–7.5 ppm (m, 11 H, 2 C_6H_5, NH).

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.64; H, 5.69; N, 4.11.

L(+)-Mandeloyl-D(−)-phenylglycine (7). To a suspension of 1.2 g (3.53 mmol) of the ester in 14 ml of methanol was added 8.0 ml of 1 *N* sodium hydroxide. After standing at room temperature for 19 hr, the solution was cooled and acidified with concentrated hydrochloric acid to pH 2.5. The precipitate was filtered and dried *in vacuo*, giving 0.791 g (79%), mp 190–194°, of the hydroxy acid: $[\alpha]^{22}D$ −120° (*c* 1.20, EtOH); ir (Nujol) 3410–3430 (OH), 3370 (NH), 1729 (COOH), 1614 cm^{-1} (-CONH–); nmr (DMSO-d_6) δ 2.07 (s, 1 H, OH), 5.07 (s, 1 H, C_6H_5CHOH), 5.38 (d, 1 H, C_6H_5CHNH), 7.18–7.55 (m, 10 H, 2 C_6H_5), 8.36 ppm (d, 1 H, NH).

Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36, H, 5.30; N, 4.91. Found: C, 67.11, H, 5.34; N, 4.99.

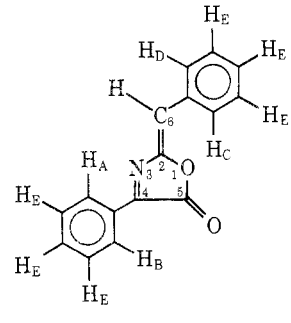
N-[O-Acetyl-D(−)mandeloyl]-D(−)-phenylglycine Methyl Ester. The method used was similar to that used for the L(+) isomer. From 2.09 g (10.4 mmol) of D(−)-phenylglycine methyl ester hydrochloride and 2.0 g (10.4 mmol) of *O*-acetyl-D(−)-mandelic acid was obtained 2.59 g (73%): mp 169–172°; $[\alpha]^{30}D$ −147° (*c* 0.52, MeOH); ir (Nujol) 3332 (NH), 1741 ($COOCH_3$, CH_3COO), 1665 cm^{-1} (-CONH–); nmr ($CDCl_3$) δ 2.16 (s, 3 H, CH_3COO), 3.68 (s, 3 H, $COOCH_3$), 5.55 (d, 1 H, C_6H_5CHNH–), 6.10 (s, 1 H, C_6H_5CHOAc), 7.18–7.45 ppm (m, 11 H, 2 C_6H_5, NH).

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.61; H, 5.72; N, 4.11.

D(−)-Mandeloyl-D(−)-phenylglycine. The procedure used for preparation of L(+)-mandeloyl-D(−)-phenylglycine was used for this isomer also. From 2.5 g (7.34 mmol) of the diester was obtained 1.85 g (88%), mp 148–150°, of the hydroxy acid: $[\alpha]^{25}D$ −112° (*c* 1.20, EtOH); ir (Nujol) 3400 (OH), 3275 (NH), 1729 (COOH), 1652 cm^{-1} (-CONH–); nmr (DMSO-d_6) δ 2.10 (s, 1 H, OH), 5.09 (s, 1 H, C_6H_5CHOH), 5.40 (d, 1 H, C_6H_5CHNH), 7.2–7.54 (m, 10 H, 2 C_6H_5), 8.40 ppm (d, 1 H, NH).

Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.09; H, 5.29; N, 4.94.

2-Benzylidene-4-phenyl-3-oxazolin-5-one (6). To 1.0 g (3.06 mmol) of **5** was added 15 ml of acetic anhydride and 1.0 ml (12.4 mmol) of dry pyridine. The yellow solution was stirred at room temperature for 1 hr and poured into ice water where it was stirred for 1 hr. Filtration gave 0.68 g (89%) of crude pseudo oxazoline, which was recrystallized from isopropyl alcohol to give 0.403 g (53%), mp 137–139° (lit.[2] mp 136–137.5°), of yellow needles: ir (Nujol) 1782 (C=O), 1645 (C=N), 1598 cm^{-1} (C_6H_5); ^1H nmr ($CDCl_3$) δ 6.43 (s, 1 H, H_F), 7.27–7.54 (m, 6 H, H_E), 7.70–7.85 (m, 2 H, H_C, H_D), 8.30–8.45 ppm (m, 2 H, H_A, H_B); ^{13}C nmr ($CDCl_3$, on crude compound) 113.67 (C_6), 128.52–132.66 (aromatic C's), 151.19 (C_2), 152.94 (C_4), 162.69 ppm (C_5); uv (95% EtOH) λ_{max} 249 nm (log ε 3.93), 258 (shoulder, 3.81), 396 (4.45), 413 (4.46).



Registry No.—(±)-**5**, 50859-91-1; L(+),D(−)-**5**, 50859-85-3; D(−),D(−)-**5**, 50859-86-4; L(+),D(−)-**5** methyl ester, 50859-87-5; D(−),D(−)-**5** methyl ester, 50859-88-6; **6**, 14389-69-6; L(+),D(−)-**7**, 50859-89-7; D(−),D(−)-**7**, 50859-90-0; *O*-acetyl-L(+)-mandelic acid, 7322-88-5; *O*-acetyl-D(−)-mandelic acid, 51019-43-3; phenylglycine, 2835-06-5; *O*-acetyl-DL-mandeloyl chloride, 49845-72-9; D(−)-phenylglycine, 875-74-1; *O*-acetyl-L(+)-mandeloyl chloride, 51019-44-4; D(−)-phenylglycine methyl ester hydrochloride, 19883-41-1; DCC, 538-75-0.

References and Notes

(1) (a) J. M. Riordan and C. H. Stammer, *Tetrahedron Lett.*, 4969 (1971); (b) *J. Org. Chem.*, in press.
(2) G. Adembri, *Ann. Chim. (Rome)*, **50**, 374 (1960).
(3) Prepared by a different method: S. Berlingozzi, G. Adembri, and G. Bucci, *Gazz. Chim. Ital.*, **84**, 383 (1954).
(4) S. H. Wilen, "Tables of Resolving Agents and Optical Resolutions," 1st ed, University of Notre Dame Press, London, 1972, p 72.
(5) W. R. Angus and R. D. Owen, *J. Chem. Soc.*, 227 (1943).
(6) E. T. Kaiser and F. W. Carson, *J. Amer. Chem. Soc.*, **86**, 2922 (1964).
(7) Prepared by treatment of the acid with thionyl chloride, bp 135° (15 mm). The acid was prepared using the procedure described in "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1948, p 12.
(8) Prepared from the acid by treatment with thionyl chloride, bp 140° (22 mm), ir (neat) 1811 (COCl), 1751 cm^{-1} (CH_3COO).
(9) M. Goodman and W. J. McGahren, *Tetrahedron*, **23**, 2301 (1967).