Cycloaddition of Chiral Nitrones. Asymmetric Synthesis of Isoxazolidines

Czeslaw Belzecki* and Irma Panfil

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44, 00-961 Warszawa, Poland

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1,3-Cycloaddition of chiral nitrones with monosubstituted olefins (or phenyl isocyanate) is diastereoselective. The products are nonracemic, diastereomeric mixtures of 2,3,5-substituted isoxazolidines. Cis isomers are formed in large excess and in each pair of cis and trans isomers, one of the diastereomers prevails. The quantitative composition of the diastereomeric mixtures has been determined. Establishment of the absolute configuration of all four isoxazolidines IX allowed for quantitative determination of the steric course of the cycloaddition.

1,3-Cycloaddition reactions of nitrones have been examined in detail and reported in a review.[1] It is generally accepted that they represent a one-step, four-centered, concerted reaction in which two new σ bonds are formed.[2] The reaction with nonsymmetric dipolarophiles, i.e., monosubstituted alkenes, is regioselective and the substituent at the ethylenic carbon atom enters position 5 of the resulting isoxazolidine ring.[3] Some exceptions to this rule, e.g., in the reactions of some alkynes, nitroalkenes, or vinyl sulfones,[4] have been explained by consideration of frontier orbital interactions.[2,5]

1,3-Cycloaddition reactions with alkenes are cis stereoselective.[2,3,6] Cis–trans isomerism observed in the cycloaddition products (isoxazolidines) concerns the substituents at positions 3 and 5. This isomerism, as well as formation of diastereomers in the case of prochiral olefins used as dipolarophiles, is a result of the approach of the reagents, i.e., 1,3-dipole of E or Z configuration and dipolarophile in an exo or endo manner.[6] Independently, in both cases the nitrone may approach either the *re* or *si* face of the olefin[7] (Scheme I, only the case of (Z)-nitrone is shown).

These features of the 1,3-cycloaddition reaction of nitrones prompted us to attempt to apply chiral nitrones (the chiral substituent at the nitrogen or carbon atom) in the asymmetric synthesis of isoxazolidines. As reported earlier,[8] these attempts were successful. We now wish to report further progress of these syntheses and the experimental details.

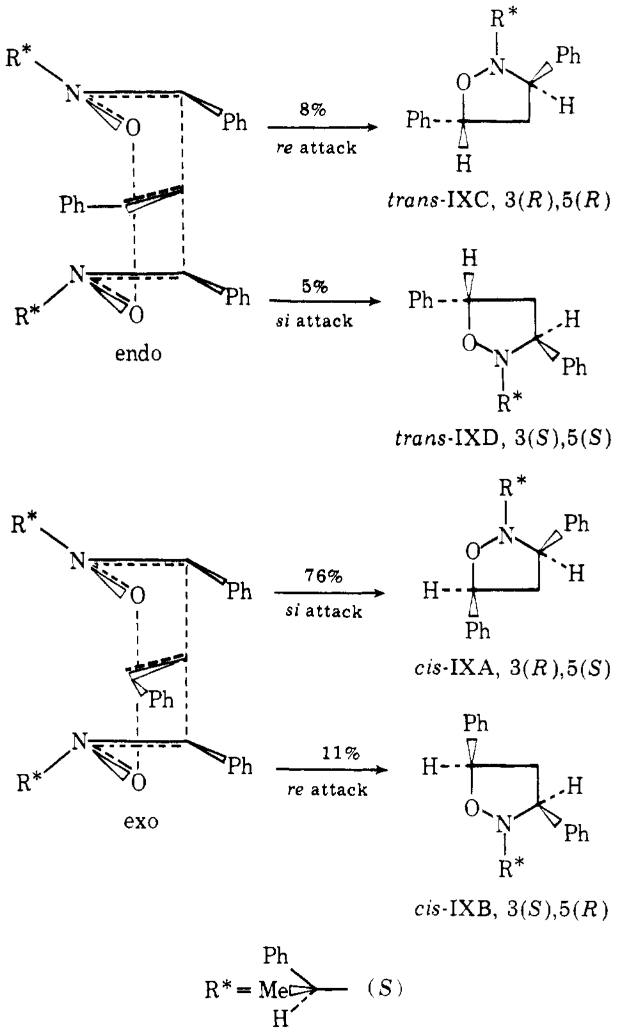
There are some earlier reports about the synthesis of chiral steroidal[9] or sugar[10] nitrones. Recently, the synthesis of chiral nitrones from chiral Schiff's bases via oxaziridines was reported.[11] The intramolecular cyclization of the nitrone from (+)-citronellal is also known, and at the same time as our experiments were in progress, the cycloaddition of the sugar chiral nitrones was published.[12]

Results

The first attempts were carried out with two racemic nitrones of Z configuration, I and II obtained by the N-alkylation of *anti*-benzaldoxime with α-bromo acids or their esters[13] (Scheme II). Both of them react easily with phenyl isocyanate, each yielding only one of the two possible diastereomeric oxadiazolidones III or IV, respectively (Scheme II).

The cycloaddition of I and II with methyl acrylate led in both cases to mixtures of diastereomeric isoxazolidines V and VI (Scheme III). The ^{1}H NMR spectrum of product V shows four signals for the ester methyl protons in the ratio of 24:23:28:15 which indicates the formation of all four possible diastereomers. Product V could be separated (preparative TLC) into two fractions in a ratio of 56:44, which correspond to the cis and trans isomers. Each of these fractions contains two diastereomers in a ratio of 67:33 and 61:39, respectively (^{1}H NMR). Unfortunately, the ^{1}H NMR spectra do not allow a conclusive assignment of relative configuration for both fractions because of overlapping signals. Adduct VI was preparatively separated into two fractions, which were pure cis and trans diastereomers in a ratio of 84:16.

Scheme I



The preliminary results showed that the reaction examined was diastereoselective and encouraged us to repeat it using chiral nitrones. The alkylation of *anti*-benzaldoxime with the chiral ester of α-bromo-β-phenylpropionic acid (obtained from L-β-phenyl-α-alanine) gave partial racemization. Optically pure nitrones were prepared by the condensation of chiral monosubstituted hydroxylamines with aldehydes. The appropriate hydroxylamines were obtained by the reaction of chiral amines with benzoyl peroxide and subsequent hydrolysis.[14] Both of the resulting nitrones VII and VIII were Z isomers (^{1}H NMR) (Scheme IV). The nitrones VII and VIII were subjected to 1,3-cycloaddition reaction with styrene,

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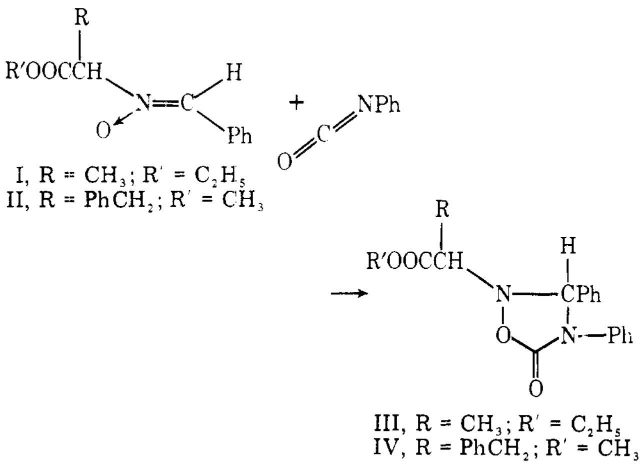
Table I

no.	nitrone	dipolarophile	product A + B + C + D	total yield, %	mixtures of diastereomers in %: cis A	cis B	cis % ee	trans C	trans D	trans % ee	cis/trans
1	VII[a]	PhCH=CH$_2$[d]	IX	90	76[g]	11[h]	75	8[i]	5[j]	23	87:13
2	VII	CH$_2$=CHCOOMe[e]	X	60	40[k]	24[l]	25	29[m]	7[n]	61	64:36
3	VII	CH$_2$=C(CH$_3$)COOMe[f]	XI	90	62[o]	20[p]	51	18[q]	0	100	82:18
4	VII	PhCH=CH$_2$	XII	85	42[r]	24[s]	27	22[t]	12[u]	34	66:34
5	XVI[c]	PhCH=CH$_2$	XVII	98	38[v]	0	100	62[w]	0	100	38:62
6	XIX	PhCH=CH$_2$	XXI	95	62[x]	6[y]	82	32[z]	0	100	68:32
7	XX	PhCH=CH$_2$	XXII	95	56[aa]	13[bb]	62	31[b]	0	100	69:31

[a–cc] Registry no.: [a] 68889-66-7. [b] 68844-57-5. [c] 68844-48-4. [d] 100-42-5. [e] 96-33-3. [f] 80-62-6. [g] 64270-60-6. [h] 64282-93-5. [i] 64270-67-3. [j] 64270-64-0. [k] 64270-62-8. [l] 64270-58-2. [m] 64270-68-4. [n] 68844-49-5. [o] 64270-61-7. [p] 64270-57-1. [q] 68844-50-8. [r] 64270-63-9. [s] 64270-59-3. [t] 64270-69-5. [u] 64270-66-2. [v] 68844-51-9. [w] 68889-68-9. [x] 68844-52-0. [y] 68844-53-1. [z] 68844-54-2. [aa] 68844-55-3. [bb] 68844-56-4.

Scheme II



I, R = CH$_3$; R′ = C$_2$H$_5$
II, R = PhCH$_2$; R′ = CH$_3$

III, R = CH$_3$; R′ = C$_2$H$_5$
IV, R = PhCH$_2$; R′ = CH$_3$

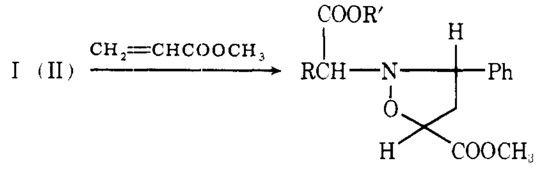
methyl acrylate, methyl methacrylate, and phenyl isocyanate (Scheme V). The quantitative results are shown in Table I (no. 1–4).

Ordinarily aldonitrones appear in the more stable Z configuration. The phenomenon of $Z \rightleftharpoons E$ isomerization has been studied and barriers for rotation about the C=N bond calculated and measured for many examples.[15,16] From this result it follows that aldonitrones show considerable configuration stability, comparable to that reported for ketonitrones. However, it cannot be excluded that under the more drastic conditions of cycloaddition (temperature) isomerization can occur and this effect may be responsible for the ratio of diastereomers formed.[6,17]

Assuming that during the cycloaddition reaction no $E \rightleftharpoons Z$ isomerization of aldonitrones takes place,[6] the diastereomers are formed as a result of the approach of reagents in an exo or endo manner as well as *re* or *si* face attack at the prochiral olefin (Table I).

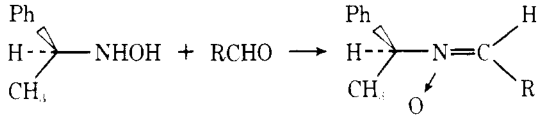
The cycloaddition reactions were carried out under relatively mild conditions (starting from room temperature up to 85 °C). Using aldonitrones VII and VIII (pure Z isomers) all four possible nonracemic diastereomeric isoxazolidines were always obtained with a clear or large excess of the cis pair. The ratio of the sum of cis (A + B) isomers to the sum of trans (C + D) isomers can be accepted as the measure of the stereospecificity of the cycloaddition, whereas the quantitative ratio within the pairs, i.e., A:B and C:D, is a measure of the diastereoselectivity and may also be expressed as % ee (enantiomer excess).

Scheme III



V, R = CH$_3$; R′ = C$_2$H$_5$
VI, R = PhCH; R′ = CH$_3$

Scheme IV



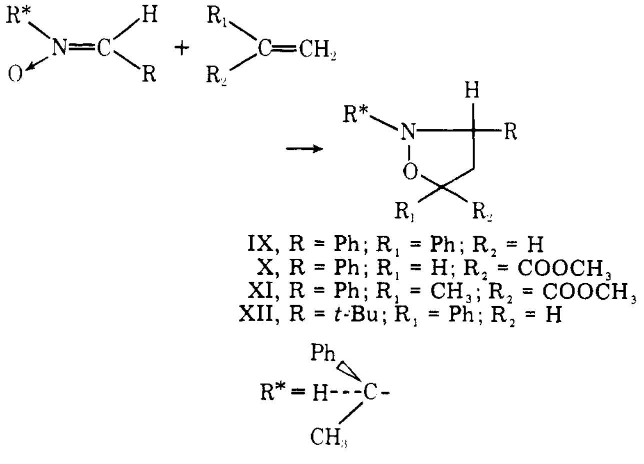
VII, R = Ph, $S(+)$
VIII, R = t-Bu, $S(-)$

The mixtures of diastereomers were separated, as far it was possible, by preparative TLC. In addition, the composition of the whole mixture as well as that of the separated fractions was quantitatively determined by integration of characteristic signals in their ^{1}H NMR spectra.

Nitrone VII and styrene gave the mixture of four diastereomers IX (A, B, C, and D, Table I); three could be separated as pure compounds. The ratio of diastereomers was 76:11 for the cis and 8:5 for the trans components of the reaction mixture. The assignment of the relative configuration was based on the analysis of the ^{1}H NMR spectra.[3] The signals of the protons at the C-4 position for compound IXA are resolved by $\Delta\delta = 2.97 - 2.15 = 0.82$ ppm, which was not observed for the trans compound IXC. The spectrum of IXB is almost identical with that of IXA.

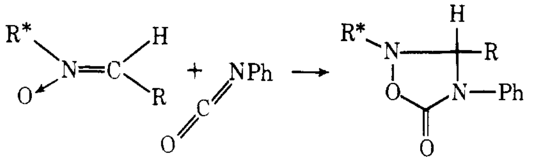
The reaction of the nitrone XII with methyl acrylate afforded a mixture of four diastereomers in a ratio of 40:25 for the cis and 29:7 for the trans pair. Two of these diastereomers,

Scheme V



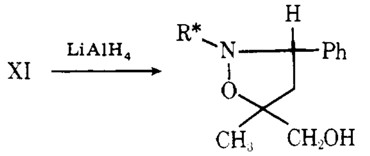
IX, R = Ph; R$_1$ = Ph; R$_2$ = H
X, R = Ph; R$_1$ = H; R$_2$ = COOCH$_3$
XI, R = Ph; R$_1$ = CH$_3$; R$_2$ = COOCH$_3$
XII, R = t-Bu; R$_1$ = Ph; R$_2$ = H

Scheme VI

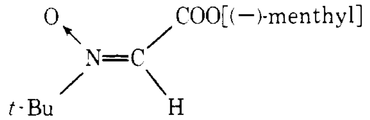


XIII, R = Ph
XIV, R = *t*-Bu

Scheme VII

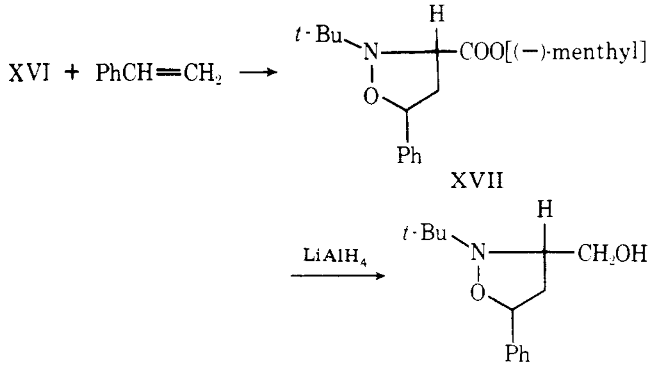


XV



XVI

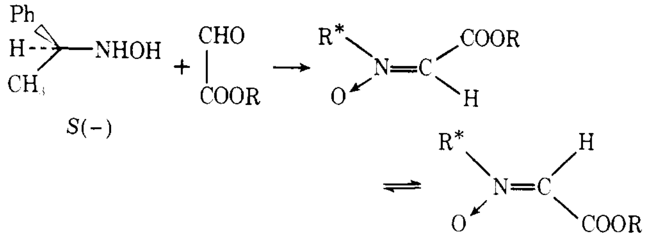
Scheme VIII



XVII

XVIII

Scheme IX



XIX, R = *n*-Bu
XX, R = CH₃

XA and XC, were separated in a pure state. Their relative configurations were assigned similarly as for IX.

The nitrone VII reacted with methyl methacrylate yielding a mixture of only three diastereomers. The presence of CH_3 and $COOCH_3$ substituents at the 5 position of the isoxazolidine ring is confirmed by the signals of the C-4 protons (two separate double doublets) and the C-3 proton (double doublet). Only one of these diastereomers, cis XIA, was isolated pure.

The nitrone VIII in cycloaddition with styrene gave a mixture of four diastereomers in a ratio of 42:24 for the cis pair and 22:12 for the trans pair (signals of *t*-Bu protons). Three products, XIIA, -B, and -C, were obtained in a pure state, and cis–trans configurations were assigned similarly as for IX. Upon carrying out the cycloaddition at temperatures ranging from 80 to 100 °C, a change in the quantitative ratio of cis–trans diastereomers from the initial value of 66:34 to 52:48 after 60 h at 100 °C takes place. Heating of pure cis diastereomer XIIA for 12 h in toluene under reflux, however, does not result in an appearance of another diastereomer. This excludes the possibility of thermodynamic equilibration of cycloaddition products at the temperature at which this reaction was carried out and, thus, it proves the kinetic control of the process.

Cycloaddition of the nitrones VII and VIII with phenyl isocyanate gives in high yield the proper 2,3,4-substituted oxadiazolidinones-5 XIII and XIV, respectively (Scheme VI). The mixture of XIII and XIV was separated preparatively (TLC). The quantitative ratios for XIII and XIV were 67:33 and 60:40, respectively, which corresponds to 34 and 20% ee.

As mentioned before, it was difficult to separate preparatively the diastereomeric isoxazolidine XI mixture (only XIA was isolated). After the reduction of the ester function, a mixture of the diastereomeric alcohols XV with the same quantitative composition was obtained (Scheme VII). However, even in this case, we were able to isolate in a pure state only the cis diastereomer, which appears in excess.

The next series of cycloaddition reactions were carried out with a nitrone containing a chiral substituent at the carbon atom of the nitrone system. The nitrone of this type XVI was obtained in the reaction of *N-tert*-butylhydroxylamine with L-(−)-menthyl glyoxalate. Cycloaddition with styrene takes place even at room temperature and yields a mixture of two of four possible diastereomers XVII in a ratio of 62:38 (Scheme VIII). This mixture could not be separated easily. The ^1H NMR spectrum of the product obtained in excess (62%) shows that it is the trans isomer, since the proton at C-3 occurs in the spectrum as a triplet, and the multiplets of the protons at C-4 are not differentiated. The second isomer (38%) possesses the cis configuration, which is shown by the double doublet of the proton at C-5 and by resolved multiplets of the C-4 protons ($\Delta\delta$ = 0.20 ppm). The isoxazolidines *cis*-XVIII as well *trans*-XVIII are epimers at C-5.

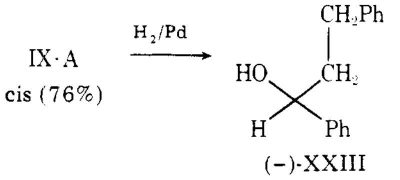
The stereochemistry of the cycloaddition leading to the excess of *trans*-XVIII is different from those previously described. It can be explained by a large steric hindrance of the carboxymenthyl substituent, which preferentially causes approach of the reagents of the dipole *Z* in an endo fashion.

The next cycloadditions were carried out with nitrones XIX and XX which carry the chiral substituent at the nitrogen atom and ester group linked to the carbon atom. They were obtained in the reaction of (*S*)-(−)-α-phenylethylhydroxylamine with *n*-butyl and methyl glyoxalate, respectively (Scheme IX). Nitrones XIX and XX showed mutarotation. The ^1H NMR for XIX revealed two signals for the $NCCH_3$ protons in a ratio changing during 3 h of the measurements from an initial value of 63:37 to 50:50. This final ratio remained constant even after heating up to 75 °C. The nitrone XX behaves similarily and it shows $Z \rightleftharpoons E$ inversion at room temperature. The failure to isolate the pure isomers by chromatography confirms this fact. The mixtures of nitrones XIX and XX were subjected to cycloaddition reactions with styrene. The resulting isoxazolidines XXI and XXII (Scheme IX) consisted of cis–cis–trans diastereomers in ratio of 62:6:32 and 56:13:31, respectively. All of them were separated and isolated in a pure state.

In order to establish the preferred stereochemistry of the cycloaddition reaction examined, it was necessary to determine the absolute configuration of the nonracemic diastereomers of isoxazolidines formed in excess in each pair of cis and trans isomers.

As a model system we chose the isoxazolidines IX. It is well

Scheme X



known that isoxazolidines of this type with aryl substituents easily undergo hydrogenolysis.[19] As a result of the hydrogenolysis of the cis diastereomer IXA formed in excess (76%), (−)-1,3-diphenylpropanol-1 XXIII was obtained. The hydrogenolysis of diastereomer *trans*-IXC (8%) gave (+)-1,3-diphenylpropanol-1 (Scheme X). The optical purity of these alcohols was determined by ^{1}H NMR integration of the methyl group signals of the ω-(−)-camphanic acid esters of these alcohols after addition to the sample of Eu(fod)$_3$.[20] The purity determined in this way was 92%.

Independently, racemic 1,3-diphenylpropanol-1 was obtained and both enantiomers were separated by the crystallization of diastereomeric esters with ω-(−)-camphanic acid. Four recrystallizations afforded the less soluble ester which after hydrolysis gave the pure enantiomer (+)-1,3-diphenylpropanol-1, $[\alpha]^{27}{}_{578}$ +28.8°. The absolute configuration of this (+)-propanol was established by Horeau's method.[21] After hydrolysis of an excess of phenylbutyric acid anhydride the resulting α-phenylbutyric acid had (*S*)-(+) configuration; consequently the alcohol investigated was (*R*)-(+)-1,3-diphenylpropanol-1.

The assignment of *S* configuration to the (−)-propanol XXIII obtained by degradation of the cis diastereomer IXA and the formation of the corresponding (+)-enantiomer by degradation of *trans*-IXC allowed the assignment of absolute configuration to all four diastereomers of IX: IXA (cis), 76%, 3(*R*),5(*S*); IXB (cis), 11%, 3(*S*),5(*R*); IXC (trans), 8%, 3(*R*),5(*R*); IXD (trans), 5%, 3(*S*),5(*S*). These results permit us to reconstruct the stereochemical course of the 1,3-cycloaddition examined which leads to the preferred diastereomers in the cis and trans pairs. On the assumption that the *Z* isomer of nitrone VII takes part in this reaction,[6] the favored approach for the cis addition is the exo approach to the *si* face of styrene (Scheme I). In the trans series, the endo approach to the *si* face of styrene is the more favorable.

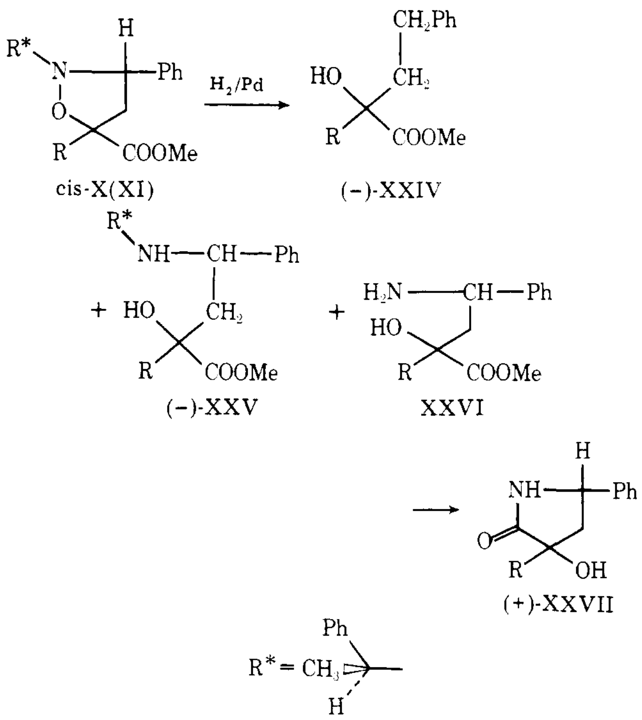
For comparison, two other cis isoxazolidines X and XI obtained in excess were subjected to hydrogenolysis under similar conditions (Scheme XI). We assumed that these diastereomers (X, R = H; or XI, R = Me) have absolute configurations analogous to the IXA compound formed in excess. The hydrogenolysis of isoxazolidines X and XI gave in both cases mixtures of three products, formed by the cleavage of different bonds as shown in Scheme XI. The following optically active compounds were separated from the mixtures: α-hydroxy ester XXIV (R = H or Me), γ-amino α-hydroxy ester XXV (R = H or Me), and hydroxylactam XXVII (R = H or Me); the latter product is a cyclization product of the intermediate α-hydroxy γ-amino ester XXVI. All these products were isolated in the pure state.

The above described reaction appears to represent a new, promising method for the asymmetric synthesis of substituted propanols, α-hydroxy esters, and 2,4-substituted pyrolidones-5.

Conclusions

The racemic nitrones obtained by alkylation of *anti*-benzaldoxime give 1,3-cycloaddition reactions with prochiral monosubstituted alkenes yielding mixtures of diastereomeric cis and trans 2,3,5-substituted isoxazolidines, with a distinct excess of the cis pair and with a clear excess of one of the diastereomers in every cis and trans pair.

Scheme XI



The chiral nitrones (chiral substituent at nitrogen or carbon atom) react analogously giving nonracemic diastereomers, which in most cases can be separated by chromatography.

Cycloaddition of chiral nitrones with phenyl isocyanate gives diastereoselectively the epimeric 2,3,4-substituted oxadiazolidones-5.

The cycloaddition process leading to cis and trans isomers is temperature dependent, but the products are thermally stable and under the cycloaddition conditions do not undergo equilibration.

Establishment of the absolute configuration of all four isoxazolidines IX allowed for quantitative determination of the steric course of the cycloaddition.

When a cycloaddition reaction occurs in the exo manner, the *si* attack at prochiral olefin predominates, whereas in the endo approach of the reagents, *re* face attack is favored.

Experimental Section

Melting points were measured on a micro hot plate and are not corrected. IR spectra were determined as films or in KBr on a Unicam SP-200 instrument. ^{1}H NMR spectra were measured with a JEOL 100MHz spectrometer and are given in δ (ppm) values. Optical rotations were measured with a Perkin-Elmer automatic photoelectric polarimeter Model 141. The microanalyses were performed in our microanalytical laboratory. TLC plates were prepared using silica gel Merck PF$_{254}$ and GF$_{254}$.

2,3,5-Substituted Isoxazolidines and 2,3,4-Substituted Oxadiazolidinones-5. General Method. Nitrone (0.01 mol), ca. 0.011 mol of olefine or phenyl isocyanate, and 10 mL of benzene were refluxed 1–15 h; the solvent and excess of reagent were removed in vacuo and products separated by TLC.

2-(1-Carbethoxy)ethyl-3,4-diphenyl-1,2,4-oxadiazolidinone-5 (III). From I and PhNCO: 4 h; yield quantitative; mp (Et$_2$O) 126–128 °C; IR (KBr) 1750 cm^{-1} (C=O); ^{1}H NMR (CHCl$_3$) 1.22 (t, 3, COOCH$_2$**CH$_3$**), 1.52 (d, 3, CH**CH$_3$**), 4.0 (q, 1, **CH**CH$_3$), 6.13 (s, 1, **CH**Ph). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.88; N, 8.23. Found: C, 66.99; H, 5.89; N, 8.24.

2-(1-Carbomethoxy-2-phenyl)ethyl-3,4-diphenyl-1,2,4-oxadiazolidinone-5 (IV). From II and PhNCO: 15 h; yield 70%; mp (Et$_2$O) 144 °C; IR (KBr) 1760 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) 3.52 (s, 3, COO**CH$_3$**), 3.92 (t, 1, CH$_2$**CH**), 3.24 (d, 2, -CH**CH$_2$**=), 6.1 (s, 1,

Table II. Specific Rotation of Isolated 2,3,5-Substituted Isoxazolidines and 2,3,4-Substituted Oxadiazolidinones-5 (*c* 1, temperature 20 °C)

no.	registry no.	solvent	$[\alpha]^{20}{}_{\lambda}$ 578	546	436	365	remarks
IXA		CH_2Cl_2	+54.4	+62.4	+110.7	+183.3	17 °C
IXB		CH_2Cl_2	−104.4	−118.8	−207.4	−313.0	
IXC		CH_2Cl_2	+35.0	+39.7	+63.5		
XA		CH_2Cl_2	−21.6	−24.6	−44.9		
XC		CH_2Cl_2	−19.2	−21.8	−37.4		
XIA		CH_2Cl_2	+10.7	+12.1	+19.0		
XIIA		CH_2Cl_2	−55.0	−64.0	−128.0	−240.0	95% purity
XIIB		CH_2Cl_2	−27.5	−31.5	−50.0	−70.5	83% purity
XIIC		CH_2Cl_2	−58.3	−66.9	−118.5	−187.5	85% purity
XIIIA	64270-70-8	CH_2Cl_2	+27.6	+32.1	+60.0		
XIIIB	64478-21-3	CH_2Cl_2	−123.0	−140.8	−255.4	−435.0	
XIVA	64270-71-9	CH_2Cl_2	+12.0	+16.2	+55.4		
XIVB	64478-22-4	CH_2Cl_2	−236.0	−270.0	−514.0	−929.0	
XVA	68844-58-6	CH_2Cl_2	+66.9	+76.7	+137.6	+233.0	17 °C
XXIA		benzene	+16.2	+16.9	+19.0	+28.5	18 °C
XXIB		benzene	−80.2	−91.4	−155.6		
XXIC		benzene	+10.5	+27.1	+51.3		18 °C
XXIIA		benzene	+13.4	+14.8	+19.6		
XXIIB		benzene	−32.5	−38.5	−63.5	−96.5	
XXIIC		benzene	+62.8	+71.8	+129.6	+219.0	

p$\mathbf{CH}$). Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.67; H, 5.51; N, 6.97. Found: C, 71.23; H, 5.45; N, 6.97.

2-(1-Carbethoxy)ethyl-3-phenyl-5-carbomethoxyisoxazolidine (V). From I and methyl acrylate: 3 h; yield 95%; oil; from diastereomers; separation TLC preparative plates using hexane–ether 70:30, developed 6×, giving two fractions, *cis*-I–*trans*-II 56:44. ^1H NMR (C_6D_6) for I: δ 3.28 and 3.32 in ratio of 39:61 (s, $COOCH_3$). ^1H NMR for II: δ 3.38 and 3.42 in ratio of 63:37 (s, $COO\mathbf{CH_3}$).

2-(1-Carbomethoxy-2-phenyl)ethyl-3-phenyl-5-carbomethoxyisoxazolidine (VI). From II and methyl acrylate: 4 h; yield 95%; oil. Separation by TLC preparative plates using hexane–ether 70:30, developed 6×, giving two diastereomers in the ratio of 86:14. Fraction I (86%) ^1H NMR (C_6D_6): δ 3.0 and 3.3 (s, 3, $COO\mathbf{CH_3}$). Fraction II (14%) ^1H NMR (C_6D_6): δ 3.1 and 3.4. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.20; H, 6.23; N, 3.79. Found: C, 68.19; H, 6.24; N, 3.72.

(*S*)-(+)-*C*-phenyl-*N*-α-phenylethylnitrone (VII). From 3.0 g (0.01 mol) of (*S*)-(−)-α-phenylethyl hydroxylamine,[14] $[\alpha]^{20}{}_{578}$ −43.5° (*c* 1, CH_2Cl_2), and 2.32 g (0.01 mol) of benzaldehyde in benzene: 5 h reflux; yield 95%; oil; IR (film) 1580 cm^{-1} (C=N), 1140 (CNO); ^1H NMR (CCl_4) δ 1.7 (d, 3, CH_3), 4.98 (q, 1, $CHCH_3$); $[\alpha]^{20}$ (*c* 1, CH_2Cl_2) (578) + 83.4°, (546) + 101.5°, (436) + 258.3°. Anal. Calcd for $C_{15}H_{15}NO$: C, 80.00; H, 6.66; N, 6.20. Found: C, 79.71; H, 6.60; N, 6.07.

(*S*)-(−)-*C*-*tert*-Butyl-*N*-α-phenylethylnitrone (VIII). From 1.38 g (0.01 mol) of (*S*)-(−)-α-phenylethylhydroxylamine and 1.44 g (0.015 mol) of trimethylacetaldehyde: 24 h at room temperature; yield 95%; mp 58 °C; IR (KBr) 1580 cm^{-1} (C=N), 1440 (CNO); ^1H NMR (CCl_4) δ 1.2 (s, 9, *t*-Bu), 1.68 (d, 3, CH_3), 4.78 (q, 1, $\mathbf{CH}CH_3$), 6.35 (s, 1, =CH–); $[\alpha]^{20}{}_{\lambda}$ (*c* 1, CH_2Cl_2) (578) −6.3°, (546) −6.6°, (436) −5.4°. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.09; H, 9.26; N, 6.82. Found: C, 76.00; H, 9.21; N, 6.90.

2-α-Phenylethyl-3,5-diphenylisoxazolidine (IX). From VII and styrene in the presence of hydroquinone: 85 °C; 15 h; yield 90%; oil; purified by preparative TLC (hexane–ether 50:50). Anal. Calcd for $C_{23}H_{23}NO$: C, 83.89; H, 6.99; N, 4.20. Found: C, 83.78; H, 7.12; N, 4.12. The mixture of diastereomers was preparatively separated (TLC, hexane–ether 99:1, developed 6×). *cis*-IXA (76%): mp 87 °C; ^1H NMR (CCl_4) δ 1.48 (d, 3, $CH\mathbf{CH_3}$), 2.15 (m, 1, 4 H_B), 2.97 (m, 1, 4 H_A), 3.8–4.15 (m, 2, $\mathbf{CH}CH_3$ and 3 H), 5.05 (t, 1, 5 H); $J_{4H_A\text{-}5H}$ = 7.5 Hz, $J_{3H\text{-}4H_A}$ = 9.2 Hz, $J_{3H\text{-}4H_B}$ = 5.0 Hz, $J_{4H_B\text{-}5H}$ = 7.4 Hz. The pure IXA was also obtained by the dissolving the whole mixture in hexane and crystallizing at −40 °C. *cis*-IXB (11%): oil; ^1H NMR (CCl_4) δ 1.48 (d, 3, $CH\mathbf{CH_3}$), 2.17 (m, 1, 4 H_B), 2.77 (m, 1, 4 H_A), 3.87–3.55 (2, $\mathbf{CH}CH_3$ and 3 H), 4.79 (t, 1, 5 H); ΔH_{AB} = 0.6. *trans*-IXC (8%): mp 82–85 °C; ^1H NMR (CCl_4) 1.52 (d, 3, $\mathbf{CH}CH_3$), 2.45 (t, 2, 4 H_{AB}), 3.85–4.15 (m, 2, 3H + $\mathbf{CH}CH_3$), 5.0 (t, 1, 5 H). Pure *trans*-IXC was also obtained as follows: after removing the *cis*-IXA from the mixture, the solvent was evaporated and the oil residue crystallized from hexane to give the pure *trans*-IXC. *trans*-IXD was not obtained in the pure state.

2-α-Phenylethyl-3-phenyl-5-carbomethoxyisoxazolidine (X). From VII and methyl acrylate: reflux for 4 h; purified on the preparative TLC plates using hexane–ether 50:50; yield 60%. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.30; H, 6.70; N, 4.50. Found: C, 73.18; H, 6.95; N, 4.37. From this mixture (four diastereomers) two diastereomers were preparatively isolated (TLC, hexane–ether 90:10, 6× developed). *cis*-XA (40%): oil; ^1H NMR (CCl_4) δ 1.50 (d, 3, $CH\mathbf{CH_3}$), 2.78 (m, 1, 4 H_A), 2.45 (m, 1, 4 H_B), ΔH_{AB} = 0.33, 2.80 (s, 3, $COO\mathbf{CH_3}$), 3.95 (q, 1, $\mathbf{CH}CH_3$), 3.16 (d, d, 1, 3 H), 4.43 (t, 1, 5 H). *trans*-XC (29%): oil; ^1H NMR (CCl_4) δ 1.46 (d, 3, $\mathbf{CH}CH_3$), 3.28 (m, 2, 4, H_{AB}), 3.63 (s, 3, $COO\mathbf{CH_3}$), 4.04 (q, 1, $\mathbf{CH}CH_3$), 4.27 (m, 2, 5 H + 3 H).

2-α-Phenylethyl-3-phenyl-5-carbomethoxy-5-methylisoxazolidine (XI). From VII and methyl methacrylate: 12 h; 70 °C; purified by TLC (hexane–ether 70:30). The obtained product (yield 90%) was a mixture of three diastereomers (H^1NMR). The preparative TLC of the mixture XI using hexane–ether 99:1 (8× developed) yielded only one pure oily diastereomer *cis*-XIA formed in excess (62%) with purity 87% (^1H NMR): IR (film) 1740 cm^{-1} (C=O), 1195 (CO); ^1H NMR (C_6D_6) δ 1.68 (d, 3, $CH\mathbf{CH_3}$), 2.03 (m, 1, 4 H_B), 3.20 (m, 1, 4 H_A), 3.43 (s, 3, $COO\mathbf{CH_3}$), 4.08 (q, 1, $\mathbf{CH}CH_3$), 4.28 (d, d, 1, 3 H); $\Delta 4H_{AB}$ = 1.17, $J_{3,4A}$ = 7.53 Hz, $J_{3,4B}$ = 5.2 Hz, $J_{H_AH_B}$ = 12.5 Hz. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.84; H, 7.07; N, 4.30. Found: C, 73.56; H, 7.05; N, 4.25.

2-α-Phenylethyl-3-*tert*-butyl-5-phenylisoxazolidine (XII). From VIII and styrene: 15 h; 85 °C; purified by TLC ($CHCl_3$). The product is a mixture of four diastereomers (^1H NMR). Separation of the whole mixture (yield 85%) by TLC (hexane–ether 98:2) yielded three diastereomers in the pure state. Anal. Calcd for $C_{21}H_{27}ON$: C, 81.55; H, 8.73; N, 4.53. Found: C, 81.54; H, 8.72; N, 4.48. *cis*-XIIA (42%): mp 89–92 °C; ^1H NMR (CCl_4) δ 1.46 (d, 3, $CH\mathbf{CH_3}$), 0.84 (s, 9, *t*-Bu), 2.80 (m, 1, 4 H_A), 1.75 (m, 1, 4 H_B), ΔH_{AB} = 0.55, 2.80 (d, 1, 3 H), 3.60 (q, 1, $\mathbf{CH}CH_3$), 4.85 (d, d, 1, 5 H). *cis*-XIIB: 83% purity (24%); oil; ^1H NMR (CCl_4) δ 1.02 (s, 9, *t*-Bu), 1.44 (d, 3, $CH\mathbf{CH_3}$), 2.3 (m, 1, 4 H_A), 1.83 (m, 1, 4 H_B), ΔH_{AB} = 0.47, 2.9 (d, 1, 3 H), 3.71 (q, 1, $\mathbf{CH}CH_3$), 4.67 (d, d, 1, 5 H). *trans*-XIIC (22%): 85% purity; mp 130 °C; ^1H NMR (CCl_4) δ 0.58 (s, 9, *t*-Bu), 1.45 (d, 3, $CH\mathbf{CH_3}$), 1.9 (m, 2, 4 H_{AB}), 2.78 (d, 1, 3 H), 3.81 (q, 1, $\mathbf{CH}CH_3$), 5.05 (t, 1, 5 H).

2-α-Phenylethyl-3,4-diphenyl-1,2,4-oxadiazolidynone-5 (XIII). From VII and phenyl isocyanate in benzene: 1 h reflux; purified by TLC chromatography (CH_2Cl_2); yield 72%. Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.74; H, 5.81; N, 8.14. Found: C, 76.53; H, 5.79; N, 7.85. The whole mixture was separated (TLC, hexane–ether–methylene chloride 10:85:5) into two epimers at C-3 in the ratio of 67:33. Epimer A (67%): mp 165 °C; ^1H NMR ($CDCl_3$) δ 1.69 (d, 3, $CH\mathbf{CH_3}$), 4.27 (q, 1, $\mathbf{CH}CH_3$), 5.76 (s, 1, 3 H). Epimer B (33%): mp 189–192 °C; ^1H NMR as for epimer A.

2-α-Phenylethyl-3-*tert*-butyl-4-phenyl-1,2,4-oxadiazolidynone-5 (XIV). From VIII and phenylisocyanate in benzene: refluxed 1 h; purified by preparative TLC (chloroform–methanol 95:5); yield quantitative. The ratio of epimers determined by integration of *t*-Bu signals in ^1H NMR spectrum. Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.07; H, 7.40; N, 8.64. Found: C, 73.92; H, 7.50; N, 8.47. IR (KBr): 1740 cm^{-1} (C=O). The epimers were separated by TLC (hexane–

ether 80:20). Epimer A (60%): mp 182 °C; ^{1}H NMR (CCl_4) δ 0.7 (s, 9, *t*-Bu), 1.56 (d, 3, $\mathrm{CH}\mathbf{CH}_3$), 3.85 (q, 1, $\mathbf{CH}\mathrm{CH}_3$), 4.45 (s, 1, 3 H). Epimer B (40%): mp 160 °C; ^{1}H NMR (CCl_4) 0.83 (s, 9, *t*-Bu), 1.61 (d, 3, $\mathrm{CH}\mathbf{CH}_3$), 3.83 (q, 1, $\mathbf{CH}\mathrm{CH}_3$), 4.53 (s, 1, 3 H).

2-α-Phenylethyl-3-phenyl-5-hydroxymethyl-5-methylisoxazolidine (XV). XI (0.325 g) and $LiAlH_4$ (0.5 g) were heated in 10 mL of ether for 0.5 h, the whole was cooled and diluted with water, and the organic layer was separated, dried, and evaporated. ^{1}H NMR spectrum of the residue shows three signals for methyl groups in the ratio of 62:20:18. One of the diastereomers, *cis*-XVA (62%), was isolated by the TLC (hexane–ether 50:50): mp 81–82 °C; IR (KBr) 3500 cm^{-1} (OH); ^{1}H NMR (C_6D_6) 1.25 (s, 3, CH_3), 1.32 (d, 3, $\mathrm{CH}\mathbf{CH}_3$), 1.8 (m, 1, 4 H_B), 2.54 (m, 1, 4 H_A), 3.32 (q, 1, $\mathbf{CH}\mathrm{CH}_3$). Anal. Calcd for $C_{19}H_{23}O_2N$: C, 76.76; H, 7.74; N, 4.71. Found: C, 76.71; H, 7.73; N, 4.24.

***C*-Carbomenthoxy-*N*-*tert*-butylnitrone (XVI).** Equimolar amounts of *tert*-butylhydroxylamine and L-(−)-menthyl glyoxalate (hydrate)[18] in benzene were heated on a water bath for 1 h and cooled; benzene was evaporated to obtain an oil product with 95% yield: IR (film) 1720 cm^{-1} (C=O), 1550 (C=N), 1170 (CO); ^{1}H NMR (C_6D_6) δ 1.08 (s, 9, *t*-Bu), 7.1 (s, 1, =CH–); $[\alpha]^{20}{}_\lambda$ (*c* 1, CH_2Cl_2) (578) −84.7°, (546) −97.1°, (436) −178°. Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.84; H, 10.24; N, 4.94. Found: C, 67.60; H, 10.11; N, 4.85.

2-*tert*-Butyl-3-carbomenthoxy-5-phenylisoxazolidine (XVII). From XVI and styrene: refluxed in benzene 1 h; purified by TLC (chloroform–methanol 99:1); yield 95%; ^{1}H NMR spectrum shows the presence of two diastereomers in the ratio of 62:38. IR (film) 1725 cm^{-1} (C=O), 1170 (CO); ^{1}H NMR (C_6D_6) 1.23 and 1.28 (s, 9, Bu), 2.55 (t, 2, 4-CH_2), 3.85 (t, 1, 5 H), 4.87 (t, 1, 3 H). Anal. Calcd for $C_{24}H_{37}NO_3$: C, 75.39; H, 9.68; N, 3.66. Found: C, 75.02; H, 9.50; N, 3.50.

2-*tert*-Butyl-3-hydroxymethyl-5-phenylisoxazolidine (XVIII). To an etheral solution of XVII was added $LiAlH_4$ (0.3 mol excess), the whole was heated for 0.5 h and cooled, water was added, and the etheral layer was separated and dried. After removing the solvent, an oily product was obtained. ^{1}H NMR spectrum shows the presence of two diastereomers in the ratio of 62:38. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.48; H. 8.94; N, 5.96. Found: C, 71.20; H, 8.86; N, 5.90. The mixture was separated by TLC (hexane–ether 50:50). *trans*-XVIIIC (62%): mp 42 °C; ^{1}H NMR (C_6D_6) δ 1.02 (s, 9, *t*-Bu), 2.12 (m, 2, 4 H_{AB}), 3.2 (m, 3, $\mathbf{CH}_2\mathrm{OH}$ and 3 H), 4.90 (t, 1, 5 H). *cis*-XVIIIA (38%): mp 54 °C; ^{1}H NMR (C_6D_6) δ 1.45 (s, 9, *t*-Bu), 1.90 (m, 1, 4 H_B), 2.10 (m, 1, 4 H_A), 3.05 (m, 1, 3 H), 3.41 (d, 2, $\mathbf{CH}_2\mathrm{OH}$), 5.0 (d, d, 1, 5 H).

***C*-Carbobutoxy-*N*-α-phenylethylnitrone (XIX).** From equimolar amounts of (*S*)-(−)-α-phenylethylhydroxylamine and *n*-butyl glyoxalate: refluxed in benzene 1 h; yield 98%; mp 66–70 °C (hexane); IR (KBr) 1720 cm^{-1} (C=O), 1560 (C=N); *m/e* 249; ^{1}H NMR (C_6D_6) (3 h after dissolving) δ 1.40 and 1.35 (d, d, 3, $\mathrm{CH}\mathbf{CH}_3$), 4.37 (q, 1, $\mathbf{CH}\mathrm{CH}_3$), 6.84 (s, 1, =CH–); $[\alpha]^{17}{}_\lambda$ (*c* 1, benzene) (mixture cis–trans 1:1) (578) −144°, (546) −170°, (436) −365°. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.46; H, 7.63; N, 5.62. Found: C, 67.07; H, 7.72; N, 5.49.

***C*-Carbomethoxy-*N*-α-phenylethylnitrone (XX).** From equimolar amounts of (*S*)-(−)-α-phenylethylhydroxylamine and methyl hemiacetal of methyl glyoxalate in benzene, 1 h reflux. The residue was crystallized from hexane–ether 50:50: yield 98%; mp 84–86 °C; IR (KBr) 1725 cm^{-1} (C=O), 1560 (C=N); ^{1}H NMR (C_6D_6) (3 h after dissolving) δ 1.42 and 1.54 (d, d, 3, $\mathrm{CH}\mathbf{CH}_3$), 3.28 and 3.48 (s, s, 3, $\mathrm{COO}\mathbf{CH}_3$), 4.48 (q, 1, $\mathbf{CH}\mathrm{CH}_3$), 6.70 (s, 1, =CH–); $[\alpha]^{17}{}_\lambda$ (*c* 1, benzene, for equilibrium cis–trans 65:35) (578) −169°, (546) −199°, (365) −427°. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.28; N, 6.76. Found: C, 63.70; H, 6.50; N, 6.70.

2-α-Phenylethyl-3-carbobutoxy-5-phenylisoxazolidine (XXI). From XIX and styrene under reflux 1 h in benzene. The product was purified by preparative TLC (ether): yield 95%; oil; IR (film) 1740 cm^{-1} (C=O), 1190 (C–O). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.78; H, 7.64;.N, 3.96. Found: C, 74.81; H, 7.70; N, 3.92. The whole mixture was separated (TLC, hexane–ether 70:30) into three diastereomers. *cis*-XXIA (62%): oil; ^{1}H NMR (C_6D_6) δ 1.70 (d, 3, $\mathrm{CH}\mathbf{CH}_3$), 2.10 (m, 1, 4 H_B), 2.62 (m, 1, 4 H_A), 3.63 (d, d, 1, 3 H), 3.95 (q, 1, $\mathbf{CH}\mathrm{CH}_3$), 5.3 (d, d, 1, 5 H). *cis*-XXIB (6%): oil; ^{1}H NMR (C_6D_6) δ 1.67 (d, 3, $\mathrm{CH}\mathbf{CH}_3$), 2.0 (m, 1, 4 H_B), 2.7 (m, 1, 4 H_A), 3.65 (d, d, 1, 3 H), 4.27 (q, 1, $\mathbf{CH}\mathrm{CH}_3$), 5.14 (t, 1, 5 H). *trans*-XXIC (32%): oil; ^{1}H NMR (C_6D_6) δ 1.64 (d, 3, $\mathrm{CH}\mathbf{CH}_3$), 2.45 (m, 2, 4 H_{AB}), 4.73 (t, 1, 5 H), 4.14 (q, 1, $\mathbf{CH}\mathrm{CH}_3$), 3.72 (t, 1, 3 H).

2-α-Phenylethyl-3-carbomethoxy-5-phenylisoxazolidine (XXII). From XX and styrene, refluxed in benzene 1 h, purified by TLC (hexane–ether 50:50). The product obtained with 95% yield is a mixture of three diastereomers (^{1}H NMR, $\mathrm{COO}\mathbf{CH}_3$). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.30; H, 6.75; N, 4.50. Found: C, 72.50; H, 6.75; N, 4.29. IR (film) 1740 cm^{-1} (C=O), 1165 (CO). Separating the mixture by TLC (hexane–ether 70:30), 4× developed, gave three diastereomers in a pure state. *cis*-XXIIA (56%): ^{1}H NMR (C_6D_6) δ 1.65 (d, 3, $\mathrm{CH}\mathbf{CH}_3$), 2.12 (m, 1, 4 H_B), 2.53 (m, 1, 4 H_A), 3.13 (s, 3, $\mathrm{COO}\mathbf{CH}_3$), 3.53 (d, d, 1, 3 H), 3.88 (q, 1, $\mathbf{CH}\mathrm{CH}_3$), 5.24 (d, d, 1, 5 H). *cis*-XXIIB (13%): oil; ^{1}H NMR (C_6D_6) δ 1.52 (d, 3, $\mathrm{CH}\mathbf{CH}_3$), 3.31 (s, 3, $\mathrm{COO}\mathbf{CH}_3$). *trans*-XXIIC (31%): mp 113–115 °C; ^{1}H NMR (C_6D_6) 1.55 (d, 3, $\mathrm{CH}\mathbf{CH}_3$), 2.43 (m, 2, 4 H_{AB}), 3.24 (s, 3, $\mathrm{COO}\mathbf{CH}_3$), 4.91 (t, 1, 5 H).

(−)-1,3-Diphenylpropanol-1 (XXIII). Hydrogenolysis of IXA. Pure diastereomer IXA (100 mg) formed in excess (76%), $[\delta]^{20}{}_{578}$ +54.4°, was diluted in 10 mL of ethanol and hydrogenated under normal pressure for 20 h over 100 mg of 10% Pd/C. The reaction was followed by TLC (hexane–ether 7:3). Then the catalyst was removed by filtration; the solvent was evaporated to obtain the crystalline (−)-1,3-diphenylpropanol-1, identical (IR, ^{1}H NMR) with the racemic synthetic sample: optical purity 92%; mp 42 °C; $[\alpha]^{20}{}_\lambda$ (*c* 1.0, CH_2Cl_2) (578) −25.7°, (546) −29.2°, (436) −47.7°, (365) −71.4°.

The hydrogenolysis of diastereomer IXC (8%), carried out analogously, gave (+)-1,3-diphenylpropanol-1: mp 42 °C; $[\alpha]^{20}{}_\lambda$ (*c* 1.0, CH_2Cl_2) (578) +24.2°, (546) +27.3°, (436) +45.6°, (365) + 68.5°.

Hydrogenolysis of Isoxazolidines X and XI (R = H or Me). The hydrogenolysis was carried out analogously as for IX. The reaction mixture was separated chromatographically (TLC preparation, $CHCl_3$–MeOH 98:2) and gave in both cases three products: Methyl 2-hydroxy-2-methyl-4-phenylbutyrate (XXIV) (R = Me): yield 40%; oil; IR (film) 1730 cm^{-1} (C=O), 3550 (OH); ^{1}H NMR (C_6D_6) δ 1.35 (s, 3, CH_3 at C-5), 3.27 (s, 3, $COOCH_3$), 2.6 and 1.95 (m, 2, m, 2, –CH_2CH_2–). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.20; H, 7.69. Found: C, 69.27; H, 7.90. The optical purity determined from the ^{1}H NMR spectrum of the ester with ω-(−)-camphanic acid was 80%: $[\alpha]^{20}{}_\lambda$ (*c* 1.0, CH_2Cl_2) (578) −38.2°, (546) −43.6°, (436) −78.0°, (365) −131.4°.

1-Carbomethoxy-1-methyl-3-phenyl-3-α-phenylethylaminopropanol-1 (XXV) (R = Me): yield 30%; oil; IR (film) 1730 cm^{-1} (C=O), 3300 (NH); ^{1}H NMR (C_6D_6) 1.1 (d, 3, $\mathrm{CH}\mathbf{CH}_3$), 1.5 (s, 3, CH_3), 3.48 (s, 3, $COOCH_3$); $[\alpha]^{20}{}_\lambda$ (*c* 1, CH_2Cl_2), (578) −13.6°, (546) −16.0°, (436) −32.5°, (365) −62.4°. Anal. Calcd for $C_{20}H_{25}O_3N$: C, 73.39; H, 7.64; N, 4.28. Found: C, 73.30; H, 7.64; N, 4.05.

3-Hydroxy-3-methyl-5-phenylpyrrolidone-2 (XXVII) (R = Me): yield 30%; mp 168 °C; *m/e* 191; IR (KBr) 1660 cm^{-1}, 1690 (C=O), 3300 (NH), 3400 (OH); ^{1}H NMR ($CDCl_3$) 1.5 (s, 3, CH_3), 2.15 (m, 1, 4 H_B), 2.55 (m, 1, 4H_A), 4.6 ppm (d, d, 3H). $[\alpha]^{20}{}_\lambda$ (c, 1, EtOH): (578) +28.7°; (546) +33.4°; (436) +63.8°; (365) +115.9°. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.10; H, 6.80; N, 7.32. Found: C, 67.74; H, 6.74; N, 6.98.

Methyl 2-hydroxy-4-phenylbutyrate (XXIV) (R = H): yield 40%; oil; IR (film) 1740 cm^{-1} (C=O), 3500 (OH); ^{1}H NMR (C_6D_6) δ 2.64 (t, 1, CH), 3.18 (s, 3, $COOCH_3$); $[\alpha]^{20}{}_\lambda$ (*c* 1, CH_2Cl_2) (578) −38.6°, (546) −44.8°, (436) −84.2°, (365) −151.6°. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.04; H, 7.21. Found: C, 67.98; H, 7.16.

1-Carbomethoxy-3-α-phenylethylamino-3-phenylpropanol-1 (XXV) (R = H): yield 30%; oil; ^{1}H NMR (C_6D_6) δ 1.36 (d, 3, $\mathrm{CH}\mathbf{CH}_3$), 3.42 (s, 3, $COOCH_3$); $[\alpha]^{20}{}_\lambda$ (*c* 1, CH_2Cl_2) (578) −39.0°, (546) −44.8°, (436) −83.7°, (365) −146.4°.

3-Hydroxy-5-phenylpyrrolidone-2 (XXVII) (R = H): yield 30%; mp 206–210 °C; *m/e* 177; IR (KBr) 3350 cm^{-1} (OH), 3200 (NH), 1680 (C=O); $[\alpha]^{20}{}_\lambda$ (*c* 1, EtOH) (578) +45.6°, (546) +53.8°, (436) + 95.8°.

(*R*)-(+)-1,3-Diphenylpropanol-1 [(+)-XXIII]. The mixture of 10 mM of racemic 1,3-diphenylpropanol-1, 15 mL of dry pyridine, and 15 mM of ω-(−)-camphanic acid chloride was allowed to stand for 48 h at room temperature. Water with ice was added and the whole extracted three times with chloroform, dried, and evaporated. The residue was diluted with ether and cooled to −15 °C to give a crude crystalline product. Three recrystallizations from ethyl ether gave pure diasteromeric ester (^{1}H NMR). The hydrolysis with 0.5 N KOH (H_2O–EtOH 1:3) for 0.5 h under reflux afforded, after the usual workup, (+)-1,3-diphenylpropanol-1. The product was purified chromatographically (TLC): mp 42 °C; $[\alpha]^{27}{}_\lambda$ (*c* 1, CH_2Cl_2) (578) +28.8°, (546) +32.7°, (436) +54.4°, (365) +81.2°.

From mother liquors, after removing the solvent and doing four recrystallizations from hexane–ether 70:30 and hydrolysis, (*S*)-(−)-enantiomer was obtained.

The Absolute Configuration of (+)-1,3-Diphenylpropanol-1 [(+)-XXIII]. Horeau Method.[20] To the solution of the (+)-alcohol XXIII (42 mg, 0.02 mM) in 1 mL of pyridine α-phenylbutyric acid anhydride (145 mg, 0.04 mM) was added. The whole was left for 24 h at room temperature and after adding 1 mL of water was left for an additional 0.5 h. Then chloroform was added to the reaction mixture, dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified chromatographically (TLC preparation). The isolated α-phenylbutyric acid possessed $[\alpha]^{20}$ +0.33° (1 mL, CH_2Cl_2), which indicate *R* configuration for the investigated (+)-1,3-diphenylpropanol-1.

Registry No.—I, 68906-28-5; II, 68906-29-6; III, 68844-59-7; IV, 68844-60-0; V, 68844-61-1; VI, 68844-62-2; XVIIIA, 68844-63-3; XVIIIC, 68844-64-4; *cis*-XIX, 68844-65-5; *trans*-XIX, 68844-66-6; *cis*-XX, 68844-67-7; *trans*-XX, 68844-68-8; (−)-XXIII, 64439-32-3; (+)-XXIII, 68889-69-0; (±)-XXIII, 68889-70-3; XXIV (R = H), 68844-69-9; XXIV (R = Me), 64270-56-0; XXIV (R = Me) ω-camphanic acid ester, 68844-70-2; XXV (R = H), 68844-71-3; XXV (R = Me), 68844-72-4; XXVII (R = H), 68844-73-5; XXVII (R = Me), 68844-74-6; phenyl isocyanate, 103-71-9; (*S*)-(−)-α-phenylethylhydroxylamine, 53933-47-4; benzaldehyde, 100-52-7; trimethylacetaldehyde, 630-19-3; *tert*-butylhydroxylamine, 16649-50-6; L-(−)-menthyl glyoxalate, 26315-61-7; *n*-butyl glyoxalate, 6295-06-3; methyl glyoxalate methyl hemiacetal, 19757-97-2.

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Oxidation of α-Amino Esters. One-Step Synthesis of Sulfenimines

E. M. Gordon* and Jelka Pluščec

The Squibb Institute for Medical Research, Princeton, New Jersey 08540

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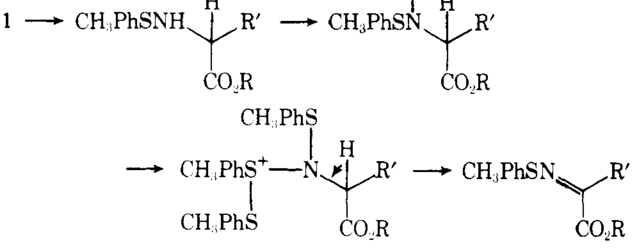
α-Amino esters (1) were oxidized to their corresponding sulfenimine derivatives (2) by mild treatment with *p*-toluenesulfenyl chloride in the presence of acid scavengers. Such amino acid derived sulfenimines are converted to α-keto esters by treatment with triphenylphosphine and silica gel. Oxidation of sulfenimines is discussed, including an example which gives rise to a dehydroamino acid residue.

The chemistry of peptide antibiotics, β-lactam antibiotics, and other peptide derived natural products is tightly interwoven with that of oxidized, dehydro, or "modified" amino acids. Consequently, the synthetic organic chemistry of amino acids (as distinct from "peptide synthesis") is an area which continues to attract increasing attention among organic chemists. Recently we observed facile sulfenyl halide initiated formation of sulfenimine (thiooxime) derivatives from esters of 6-aminopenicillanic and 7-aminocephalosporanic acids.[1] The structural and chemical similarity of such β-lactam nuclei to classical amino acids suggested that our methodology should be applicable to this class of compounds. Amino acid derivatives resulting from such reactions would have oxidation states equivalent to the dehydro amino acid level and, therefore, hold promise as useful synthetic intermediates. We now wish to report that amino acid esters (1) can be oxidized by *p*-toluenesulfenyl chloride (TSC) to sulfenimine derivatives of type 2.

The general procedure for this transformation is as follows. Amino acid ester hydrochloride salts are converted to their free bases with triethylamine and treated with 3 molar equiv of TSC[2] in dry methylene chloride at 0–5 °C. One or more acid scavengers such as pulverized molecular sieves,[3] propylene oxide, or anhydrous potassium carbonate are employed to trap liberated hydrogen chloride. Sulfenimines (2) form rapidly and were obtained in pure form (51 to 95% isolated yield) following silica gel chromatography to remove coproduced *p*-tolyl disulfide. The products were isolated as stable, yellow-orange oils or low melting solids, except for glycine derivative 8 which was obtained as a mobile liquid. Representative examples of this reaction are summarized in Table I. With cysteine ethyl ester (7) simultaneous sulfenylation of the sulfhydryl group occurred to afford a mixed disulfide. Free carboxylic acids of type 2 may also be prepared by a modified procedure. Thus silylation [2 equiv of bis(trimethylsilyl)acetamide, CH_2Cl_2, 1 h] of thienyl glycine, followed by reaction with TSC and subsequent hydrolysis, afforded sulfenimine acid **9**.[4]

We propose that sulfenimines 3–8 arise by the mechanism outlined in Scheme I. Initial *N*-sulfenylation to form a sulfenamide is analogous to the well-known protection of amino acids with *o*-nitrophenylsulfenyl chloride. Further *N*-sulfenylation followed by *S*-sulfenylation, and subsequent elimination, account for the observed products. Support for this pathway comes from another investigation in which we

Scheme I



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