Behaviour of Aminoacids and Aliphatic Aldehydes in Dipolar Aprotic Solvents: Formation of Oxazolidinones

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Reactions of aliphatic branched aldehydes with proline in dimethyl sulfoxide or acetonitrile solution afford oxazolidin-5-ones with high diastereoselection. Linear aldehydes afford aldolic/crotonic condensation products; with short reaction times, the presence of oxazolidinones can be detected in the pmr spectra. Acyclic aminoacids and branched aldehydes yield a reaction mixture the pmr and ir spectra of which give evidence for iminic-oxazolidinone equilibria. The structure of (2*R*,5*S*)-2-trichloromethyl-1-aza-3-oxabiciclo-[3.3.0]octan-4-one has been confirmed by X-ray diffraction analysis.

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Introduction.

We have previously described the synthesis of 1-oxapyrrolizidines, 1,3-oxazolidines and pyrrolizidines by the cycloaddition reaction of carbonyl and ethylenic dipolarophyles with azomethineylides synthesized from proline and aromatic aldehydes in aprotic dipolar solvents [1].

In this paper we report the products formed by the reaction of aminoacids with aliphatic aldehydes in acetonitrile and dimethylsulfoxide.

Results and Discussion.

Chemical Reactions.

The results obtained with L-proline with isobutanal, 2-methylbutanal, pivalaldehyde, and trichloroacetaldehyde are summarized in Figure 1.

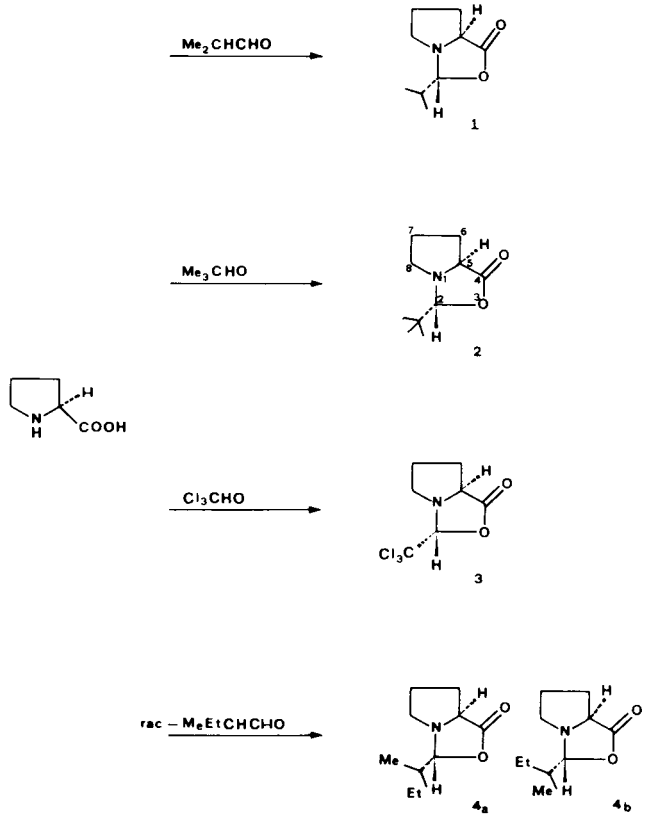

Figure 1

Addition of a 2.5 molar excess of isobutanal to a suspension of proline in dimethyl sulfoxide results in a homogeneous solution; pmr and cmr spectra of the crude reaction mixture in dimethyl sulfoxide-d_6 give evidence for the formation of oxazolidinone **1** as a single diastereoisomer. Similarly pivalaldehyde and proline in dimethylsulfoxide gives **2**, again as a single diastereoisomer, as shown by spectroscopic investigation of the reaction mixture. Compound **2** had been previously obtained from pivalaldehyde with the trimethylsilylester of *N*-trimethylsilylproline [2] and, more recently, with proline under acid catalysis in a hydrocarbon solvent [3].

Attempts to isolate oxazolidinones **1** and **2** from the dimethyl sulfoxide solution were unsuccessful, as these compounds are very sensitive to hydrolysis and reform L-proline with unchanged optical activity.

In contrast L-proline reacts with trichloroacetaldehyde in acetonitrile yielding **3** in 75% yield. Hydrolysis in aqueous ethanolic solution leads to L-proline as verified by the value of the optical rotation and by thin-layer chromatography analysis based on ligand exchange [4]. This result proves that no racemization occurs at C-5 during the condensation. The relative stereochemistry, that is the configuration at C-2, has been determined by X-ray diffraction analysis, as discussed later. In the synthesis best results were obtained with acetonitrile as the solvent; reaction of proline with dry trichloroacetaldehyde in the absence of any solvent or in benzene with azeotropic removal of water gave poorer results [5]. For isobutanal and pivalaldehyde, which in acetonitrile dissolve with difficulty and react sluggishy, dimethyl sulfoxide was found to be a more suitable solvent.

L-Proline and racemic 2-methylbutanal affords two diastereoisomeric products **4a** and **4b** in equimolecular amounts. The pmr spectrum of the crude material exhibits two 1:1 doublets centered at δ 4.88 and 4.85 (J = 7.5 Hz), corresponding to the hydrogens in position 2 of the two diastereoisomers (Figure 1). The H-5 is also differentiated and gives rise to two 1:1 doublets of doublets centered at δ 3.89 and 3.84 (J = 6.8 Hz), respectively. These data are consistent with two diastereoisomers having the same configuration at the oxazolidine ring: the chemical shift of H-2 and H-5 is in fact strictly dependent on the configuration of the corresponding carbon atoms as shown for the previously synthesized 1-oxapyrrolizidine [1]. Since no diastereoselection was observed at the enantiotopic center of the aldehyde, the reaction pathway "a" (Figure 2) seems more likely than pathway "b".

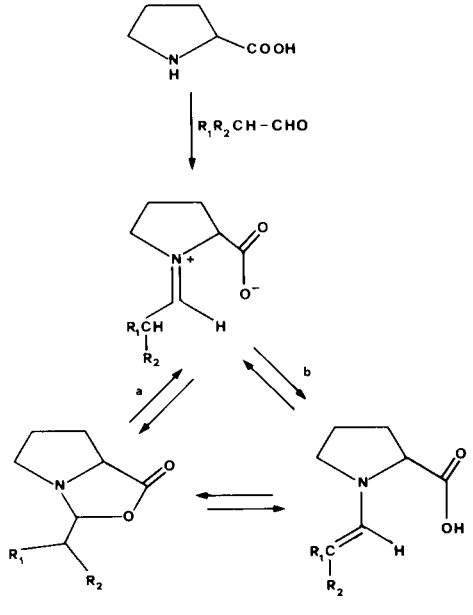

Figure 2

The use of linear aldehydes, in place of branched aldehydes affords aldolic and/or crotonic condensation depending on the reaction times and on the aldehyde-to-proline mole ratios. Both propanal and butanal afford mixtures of diastereoisomeric aldols in similar amounts. However, with short reaction times, the presence of the oxazolidinone can be detected in the pmr spectrum of the reaction mixture obtained form proline and butanal [δ 5.18 (t, 1H, J = 7.5 Hz, H-3)].

Recently MNDO calculations suggests the involvement of oxazolidinones in the decarboxylative route to azomethineylides [6]. The observed decomposition of **3**, when treated under the same conditions which usually afford oxazolidines and pyrrolizidines, seems to rule out this involvement. However, this decomposition behaviour of **3** could be attributable to a decreased ability of the trichloromethyl group (relative to a phenyl group) in stabilizing the negative charge which is the "driving force" of the formation for the azomethine ylide.

The results obtained with proline prompted us to investigate the behaviour in organic solvents of aliphatic aldehydes with acyclic aminoacids without *N*-substituents. Spectroscopic and polarimetric investigations in aqueous solutions indicate the existence of *p*H dependent equilibria involving various species [7]. When the reaction is performed in dimethyl sulfoxide, isobutanal shows different behaviours depending on the aminoacid used. No reaction is observed in the presence of glycine and alanine, even after a long time, whereas isobutanal condense with valine, leucine and phenylalanine within approximately one hour. The pmr spectra (dimethyl sulfoxide-d_6) of the reaction mixtures are characterized by the presence of a broad signal in the range δ 5.8-6.1. These values are shifted upfield with respect to those reported in the literature for iminic hydrogens (which usually fall in the range δ 6.7-7.5), but the assignment to the iminic proton Ha (Figure 3) has been confirmed by spin decoupling experiments which correlate Ha to Hb. The position and broadness of the signal point to the presence of a prototropic

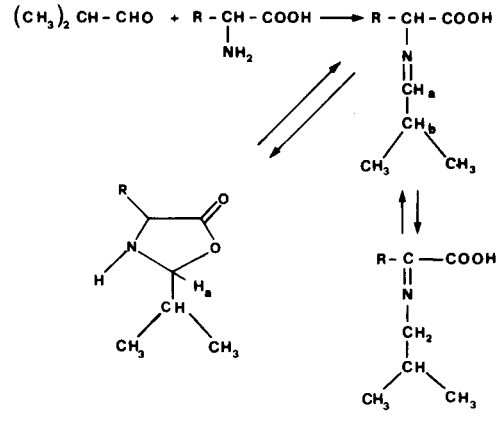

Figure 3

equilibrium. Since hydrolysis of the reaction mixture affords the starting aminoacids with unchanged chirality a iminic-iminic equilibrium should be excluded, whereas an equilibrium between the imine and the oxazolidinone is most likely. This is supported by the ir spectra which show a strong absorption band at 1775 cm^{-1}. The imine-oxazolidinone equilibrium is characteristic of aliphatic aldehydes. In contrast, aromatic aldehydes, *e.g.* *p*-nitrobenzaldehyde reacts with glycine, alanine, leucine and phenyl alanine in dimethyl sulfoxide to give the corresponding imine, as shown by a singlet at 8-8.5 ppm in the pmr spectra, by an absorption band at 1630 cm^{-1} (stretching C=N) in the ir spectra and by a doublet at 161 ppm in the cmr spectrum of the leucine derivative. Complete racemization is observed with phenylalanine after 8 hours, as the greater acidity of the hydrogen atom linked at the chiral carbon favors the iminic-iminic equilibrium and depresses the formation of the oxazolidinone.

Single Crystal X-Ray Study of Compound **3**.

Analysis of this compound was carried out as a proof of the stereochemistry at C-2, as chemical evidence of the *S*-configuration at C-5 has been given as described above.

The X-ray crystal data are summarized in Table 1.

Table 1

Crystal Data

Formula	$C_7H_8NO_2Cl_3$
M	244.5
Space group	$P2_12_12_1$
Crystal system	Orthorombic
a/Å	13.023 (3)
b/Å	9.024 (2)
c/Å	8.725 (2)
U/Å	1025.4
Z	4
Dc/Mgm^{-3}	1.58
F(000)	496
Radiation (λ/Å)	(MoKα (0.7107))
Reflections measured	1200
Scan method	θ/2θ
Scan speed/° min^{-1}	1.8
Scan width/°	1.2
Background counts per s of counting time	20
2θmax/°	50
σ limit [I > n σ(I)]	n=3
Unique observed reflections (I > 3 σ(I))	896
Weighting scheme w	$3.8699[\sigma^2(F0)+0.000169(F0)^2]^{-1}$
$R = (\Sigma [\mid Fo \mid - \mid Fc \mid] / \Sigma \mid Fo \mid)$	0.0362
$Rw = \frac{\Sigma w^{1/2}[\mid Fo \mid - \mid Fc \mid]}{\Sigma w^{1/2} \mid Fo \mid}$	0.0401

A perspective view of the molecular structure with the atom numbering scheme is shown in the ORTEP drawing of Figure 4. The two five-membered rings have different conformations. Ring B assumes a half-chair conformation with $D_2N(1)$ of 0.049(2) Å and with puckering parameters [8] q_2 = 0.374(6) Å and ϕ_2 = 102.9(8) whereas ring A is rather flat, with deviations from its best mean plane ranging from −0.040(4) Å to 0.069(4) Å and with q_2 and ϕ_2

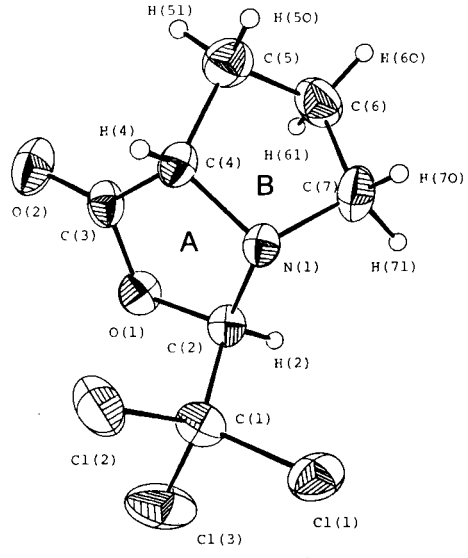

Figure 4

Table 2

Relevant Bond Lenghts (Å) and Angles (°) with e.s.d.'s in Parentheses

a) Bonds			
Cl(1)-C(1)	1.765(5)	Cl(2)-C(1)	1.763(5)
Cl(3)-C(1)	1.782(5)	N(1)-C(2)	1.426(5)
N(1)-C(4)	1.474(6)	N(1)-C(7)	1.490(7)
O(1)-C(2)	1.434(5)	O(1)-C(3)	1.363(5)
O(2)-C(3)	1.188(6)	C(1)-C(2)	1.531(7)
C(3)-C(4)	1.500(6)	C(4)-C(5)	1.524(8)
C(5)-C(6)	1.508(9)	C(6)-C(7)	1.508(8)
b) Angles			
C(4)-N(1)-C(7)	106.4(4)	C(2)-N(1)-C(7)	115.9(4)
C(2)-N(1)-C(4)	106.9(3)	C(2)-O(1)-C(3)	109.4(3)
Cl(2)-C(1)-Cl(3)	110.9(3)	Cl(1)-C(1)-Cl(3)	107.9(3)
Cl(1)-C(1)-Cl(2)	109.4(3)	Cl(3)-C(1)-C(2)	109.0(3)
Cl(2)-C(1)-C(2)	110.9(3)	Cl(1)-C(1)-C(2)	108.7(3)
O(1)-C(2)-C(1)	107.4(3)	N(1)-C(2)-C(1)	113.0(4)
N(1)-C(2)-O(1)	108.9(3)	O(2)-C(3)-C(4)	129.8(4)
O(1)-C(3)-O(2)	121.1(4)	N(1)-C(4)-C(3)	104.8(4)
O(2)-C(3)-C(4)	129.8(4)		
O(1)-C(3)-C(4)	109.1(4)		
C(3)-C(4)-C(5)	112.7(4)		
N(1)-C(4)-C(5)	107.2(4)		
C(4)-C(5)-C(6)	103.4(5)		
C(5)-C(6)-C(7)	102.1(5)		
C(1)-C(7)-C(6)	106.1(4)		

Table 3

Atomic Coordinates (10^4) for Non Hydrogen Atoms and U Equivalent (10^3) with e.s.d.'s in Parentheses for **3**

	x/a	y/b	z/c	Ueq
Cl(1)	4889(1)	3675(1)	4908(2)	77(1)
Cl(2)	3264(1)	2878(2)	2826(2)	92(1)
Cl(3)	2798(1)	4056(2)	5863(3)	113(1)
N(1)	4301(2)	361(4)	4632(4)	48(1)
O(1)	2618(2)	809(3)	5400(3)	55(1)
O(2)	1776(3)	−962(4)	4153(4)	81(1)
C(1)	3642(4)	2921(6)	4766(6)	63(2)
C(2)	3651(3)	1358(5)	5449(5)	46(1)
C(3)	2568(3)	−0365(5)	4420(5)	54(1)
C(4)	3626(3)	−0694(5)	3828(5)	51(1)
C(5)	3990(5)	−2248(6)	4244(8)	72(2)
C(6)	4501(5)	−2034(7)	5779(8)	77(2)
C(7)	5012(4)	−547(6)	5586(7)	70(2)

values of 0.165(8) Å and 73(2)°, respectively. The dihedral angle between the best mean planes of the two rings is 68.1(2)°. The carbonyl group, coplanar with the A ring, essentially retains double bond character with a C(3)-O(2) distance of 1.188(6) Å. However, some electron delocalization extending to the C(3)-O(1) bond is suggested by the C(3)-O(1) bond length [1.363(5) Å] which is shorter than the C(2)-O(1) bond length [1.434(5) Å]. The two protons, H-4 and H-2, occupy *trans* positions relative to the junction of the two pentaatomic rings, as shown by the values of the torsion angles C(2)-N(1)-C(4)-H(4) [114(3)°] and C(4)-N(1)-C(2)-H(2) [129(3)°] and by the deviations from the best mean plane [H(2): −0.63(4) Å and H(4):0.79(4) Å] of the A ring. The N(1) lone pair (as inferred from the orientation of N(1)) is *cis* to H(4) and consequently *trans* to H(2). Two of the C-Cl bond distances are essentially equal [C(1)-Cl(2) 1.763(5) Å and C(1)-Cl(1) 1.765(5) Å] while one is longer [C(1)-Cl(3) 1.782(5) Å], probably due to steric requirements.

The molecular packing is shown in Figure 5. The molecules are arranged to form puckered rows of head-to-head pairs, with the C(5)-C(6) bonds of neighboring molecules facing each other and the -CCl "tails" fitting in a staggered conformation. Adjacent rows interact with one another along the C axis, giving rise to a sort of polymeric arrangement, as schematically illustrated in Figure 5. A molecule in the center row is oriented so that its O(2) carbonyl oxygen and H(4) hydrogen are directed toward the H(2)′ and O(1)′ atoms respectively of the molecule in the adjacent lower row (′ = ½ -x, -y, -½ + z) and, in turn H(2) is directed toward O(2)″ and O(1) toward H(4)″ of the upper row (″ = ½ -x, -y, ½ + z). The intermolecular distances, O(2)...H(2)′ = 2.50 Å and H(4)G...O(1)′ = 2.61 Å are within the limits of weak oxygen-hydrogen interactions.

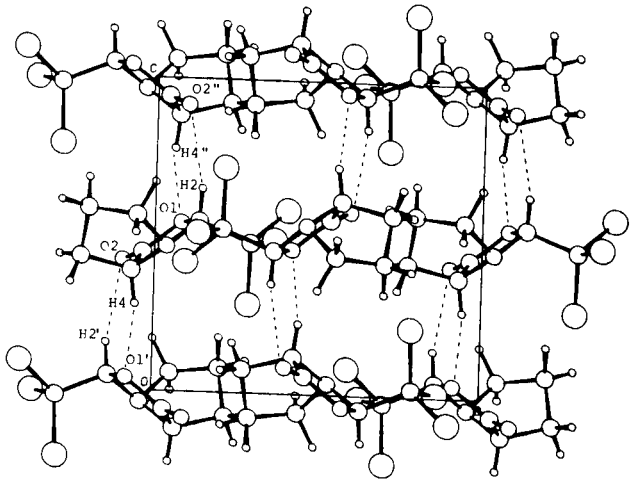

Figure 5

EXPERIMENTAL

Starting Materials.

Acetonitrile (from C. Erba) was purified by distillation over phosphorus pentoxide. Dimethyl sulfoxide-d_6 (DMSO-d_6 99.8%, Merck) was stored over 4A Molecular Sieves (conditioned at 200° and 1 mm Hg) and directly used.

General Methods.

Infrared (ir) spectra were recorded in either dimethyl sulfoxide-d_6 or deuteriochloroform using a Perkin Elmer 457 spectrophotometer. Proton nuclear magnetic resonance (pmr) and carbon-13 nuclear magnetic resonance (cmr) spectra were recorded in dimethyl sulfoxide-d_6 or deuteriochloroform with tetramethylsilane (TMS) as the internal standard, using a Brucker WP 80 pulsed FT spectrometer. The pmr spectra are reported as δ values in ppm relative to TMS; cmr chemical shifts are reported as ppm relative to TMS. Mass spectra were recorded on a VG 7070 EQ instrument. All reactions were carried out under anhydrous conditions in a nitrogen atmosphere.

X-Ray Analysis.

The X-ray structure of compound **3** was determined on a Philips PW 1100 diffractometer using graphite-monochromated Mok radiation (λ = 0.71069 Å). Cell constants were determined by least square fitting of the setting angles of the diffractometer between 20° and 26°. Intensity data were collected at room temperature (293 ±2K) and corrected for Lorentz and polarization factors but not for absorption. The structure was solved with SHELX 76 [9] program using direct methods and refined by least squares techniques. The hydrogen atom positions were derived from difference maps. All non-hydrogen atoms were refined anisotropically, while the hydrogens were refined isotropically. The number of parameters refined in the final cycles was 150. Final atomic coordinates are given in Table 3. Atomic scattering factors were taken from reference [10].

(2*R*,5*S*)-2-Isobutyl-1-aza-3-oxabicyclo[3.3.0]octan-4-one, **1**.

Isobutanal (0.022 g, 0.3 mmole) was added to a suspension of

proline (0.023 g, 0.2 mmole) in dimethyl sulfoxide-d_6 (0.5 ml) and the mixture was stirred overnight. The resulting solution was filtered (Millipore HV 0.45 micron) into a nmr test tube. After recording the pmr spectrum, the same solution was diluted with dimethyl sulfoxide-d_6 (0.5 ml) and the ir spectrum was recorded; ir: ν 1775 cm^{-1}; pmr: δ 4.81 (d, 1H, J = 7.5 Hz), 3.80 (dd, 1H, J = 6.0, 8.0 Hz), 3.06 (ddd, 1H, J = 10.5, 7.5, 7.5 Hz), 2.77 (ddd, 1H, J = 10.5, 7.5, 7.5 Hz), 2.3-1.6 (m, 5H), 1.00 (d, 3H, J = 7.5 Hz), 0.87 (d, 3H, J = 7.5 Hz).

(2*R*,5*S*)-2-(*t*-Butyl)-1-aza-3-oxabiciclo[3.3.0]octan-4-one, **2**.

The reaction between proline and pivalaldehyde was carried out as described for proline and isobutanal; ir: ν 1775 cm^{-1}; pmr: δ 4.67 (s, 1H), 3.83 (dd, 1H, J = 6.0, 8.0 Hz), 3.01 (ddd, 1H, J = 10.0, 7.5, 7.5 Hz), 2.86 (ddd, 1H, J = 10.0, 7.5, 7.5 Hz), 2.3-2.0 (m, 2H), 1.9-1.6 (m, 2H), 0.89 (s, 9H).

(2*R*,5*S*)-2-Trichloromethyl-1-aza-3-oxabiciclo[3.3.0]octan-4-one, **3**.

Dry trichloroacetaldehyde (0.25 ml, 2.6 mmoles) was added to a suspension of L-proline (0.30 g, 2.6 mmoles) in dry acetonitrile (8 ml) and the mixture was stirred overnight at room temperature. The solvent was evaporated *in vacuo* to give a solid residue; this, after crystallization from ethanol gave **3** (colorless prisms 75% yield) mp 109-110°; $[\alpha]_D^{25}$ = +32.5 (c = 2, C_6H_6); ir (chloroform): ν 1805, 1450, 1320, 1180 cm^{-1}; pmr (deuteriochloroform): δ 5.13 (s, 1H), 4.10 (t, 1H, J = 7.0 Hz), 3.6-3.0 (m, 2H), 2.3-1.7 (m, 4H); pmr (dimethyl sulfoxide-d_6): δ 5.82 (s, 1H), 4.10 (dd, 1H, J = 8.6 Hz), 3.4-3.1 (m, 2H), 2.3-1.7 (m, 4H) cmr (deuteriochloroform): 175.4 (s), 103.7 (d), 100.8 (s), 62.4 (d), 57.9 (t), 30.0 (t), 25.4 (t); ms: (70 eV, electron impact) m/e 248-246-244 (molecular ion), 220-218-216, 204-202-200, 126, 98.

Anal. Calcd. for $C_7H_8NO_2Cl_3$: C, 34.35; H, 3.27; N, 5.72. Found: C, 34.32; H, 3.29; N, 5.69.

Reaction of Isobutanal with Phenylalanine.

Isobutanal (0.022 g, 0.3 mmole) was added to a suspension of phenylalanine (0.033 g, 0.2 mmole) in dimethyl sulfoxide-d_6 (0.5 ml) and the mixture was warmed to 40°. The resulting solution was treated with a small quantity of 4A Molecular Sieves and stirred for a few minutes. The reaction mixture was filtered (Millipore HV 0.45 micron) into a nmr test tube and the pmr spectrum was recorded. The solution was then diluted with dimethyl sulfoxide-d_6 (0.5 ml) and the ir spectrum recorded: ir: ν 3500, 2980-2880, 1770, 1720, 1670, 1605, 1500, 1470, 1450 cm^{-1}; pmr: δ 7.20 (m, 5H), 6.05 (br s, 1H), 3.80 (dd, 1H, J = 4.5, 9 Hz), 2.84 (dd, 1H, J = 9.0, 13.5 Hz), 3.06 (dd, 1H, J = 4.5, 13.5 Hz), 2.84 (dd, 1H, J = 9.0, 13.5 Hz), 2.03 (m, 1H), 0.85 (d, 3H, J = 7.0 Hz), 0.84 (d, 3H, J = 7.0 Hz).

Reaction of Isobutanal with Valine.

The reaction was carried out as described for isobutanal and phenylalanine; ir (dimethylsulfoxide): ν 3500, 2980-2880, 1775, 1720, 1670, 1470 cm^{-1}; pmr (dimethylsulfoxide): δ 6.00 (m, 1H), 3.31 (d, 1H, J = 6.0 Hz), 1.99 (m, 1H), 1.05 (d, 3H, J = 7.0 Hz), 0.95 (d, 3H, J = 7.0 Hz), 0.90 (d, 3H, J = 7.0 Hz), 0.83 (d, 3H, J = 7.0 Hz).

Reaction of Isobutanal with Leucine.

The reaction was carried out as described for isobutanal and phenylalanine; ir (dimethyl sulfoxide-d_6): ν 3500, 2980-2880, 1765, 1720, 1665, 1470 cm^{-1}; pmr (dimethyl sulfoxide-d_6): δ 5.80 (m, 1H), 3.55 (dd, 1H, J = 6.0, 3.0 Hz), 2.03 (m, 1H), 1.62 (m, 1H), 1.47 (m, 2H), 0.95 (d, 3H, J = 7.0 Hz), 0.94 (d, 3H, J = 7.0 Hz), 0.88 (d, 3H, J = 7.0 Hz), 0.84 (d, 3H, J = 7.0 Hz); cmr: 176.30 (s), 60.70 (d), 32.25 (d), 24.27 (d), 22.90 (d), 21.27 (q), 18.10 (q), 17.91 (q).

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