Sterically Controlled Syntheses of Optically Active Organic Compounds. XVII. Asymmetric Syntheses of Amino Acids by Addition of Benzoyl Cyanide to the Azomethine Compounds[1]

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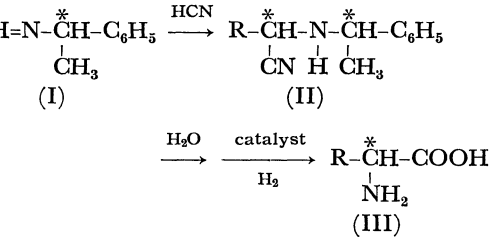
The addition reactions of benzoyl cyanide to the Schiff's bases prepared from several aliphatic aldehydes with optically active benzylic amines were studied. The adioditn products were hydrolyzed and hydrogenolyzed to form optically active amino acids. The synthetic yields of optically active amino acids were in a range 15 to 57% and the optical purities were in a range 15—37%. When *S*-α-alkylbenzylamines were used, *S*-amino acids were obtained.

Addition reactions to the cabon-nitrogen double bonds have been studied.[2,3] Carbon-nitrogen double bonds react with hydrogen cyanide to form α-aminonitriles.[4-12] Hydrolysis of the aminonitriles yielded α-amino acids.

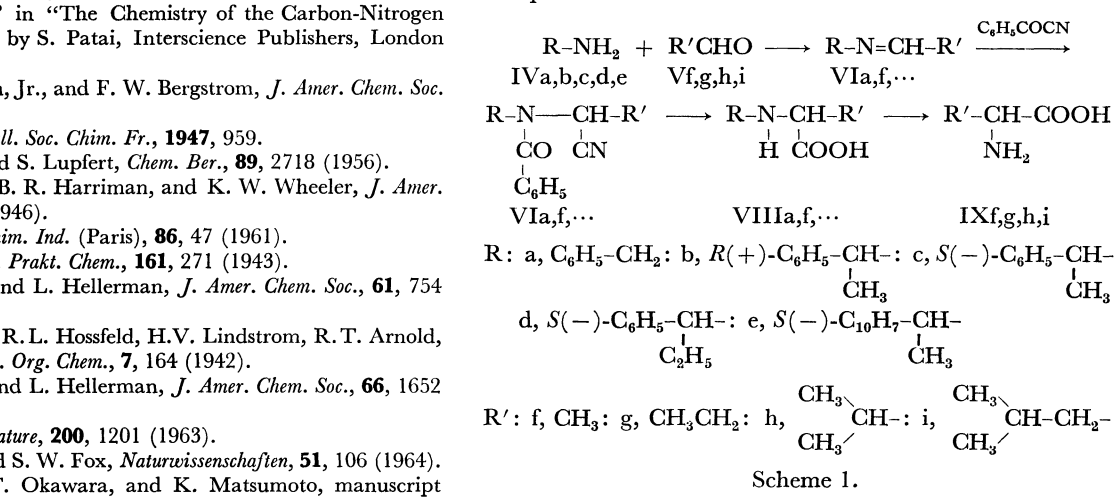
Partially optically active *N*-alkyl-α-aminopropionitrile (II) was prepared from optically active α-methylbenzylamine, acetaldehyde, and hydrogen cyanide[13] or from the same amine with lactnitrile.[14] *N*-α-Methylbenzyl aminoacetonitrile (II) was hydrolyzed and hydrogenolyzed to form optically active alanine. From the reaction mixture, highly optically active alanine (optical purity 85—98%) was isolated by crystallization in which fractionation of optical isomers would take place.[15]

Recently Patel and Worsley[16] reported an asymmetric synthesis of α-amino acids (mostly unnatural) by addition of hydrogen cyanide to the carbon-nitrogen double bond of the Schiff's base that was prepared from optically active α-methylbenzylamine and various aldehydes. The optical purities of amino acids they reported were very high (98—99%). The high optical purities have resulted from fractionation during the crystallization and washing procedures employed in the synthesis.[17]



In this investigation, the addition reactions of benzoyl cyanide to azomethine compounds prepared from various optically active benzylic amines and aliphatic aldehydes were studied as shown in Scheme 1. The amines used were benzylamine, *S*-(−)-α-methylbenzylamine, *R*(+)-α-methylbenzylamine, *S*(−)-α-ethylbenzyl amine, and *S*(−)-α-(1-naphthyl)ethylamine. The aldehydes used were acetaldehyde, propionaldehyde, isobutyraldehyde, and isovaleraldehyde.

The addition reactions of benzoyl cyanide to the various azomethine compounds were carried out at room temperature in ether solution for 20—24 hrs. The



Scheme 1.

1) Contribution No. 224 of the Institute for Molecular and Cellular Evolution, University of Miami.

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17) K. Harada and T. Okawara, manuscript in preparation.

TABLE 1. RACEMIC *N*-BENZYLAMINO ACIDS

N-Benzyl-(±)-amino aicd	Formula	Mp (°C)	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
$C_6H_5CH_2NHCH(CH_3)COOH$	$C_{10}H_{13}NO_2$	250—253	67.02	7.31	7.82	66.81	7.30	7.59
$C_6H_5CH_2NHCH(CH_3)CH_2COOH$	$C_{11}H_{15}NO_2$	245—246	68.37	7.82	7.25	68.27	7.82	7.25
$C_6H_5CH_2NHCH(CH(CH_3)_2)COOH$	$C_{12}H_{17}NO_2$	248—249	69.54	8.27	6.76	69.28	8.16	6.49
$C_6H_5CH_2NHCH(CH(CH_3)_2)CH_2COOH$	$C_{13}H_{19}NO_2$	224	70.56	8.65	6.33	70.37	8.51	6.15

resulting reaction products that contained *N*-benzoyl-*N*-alkylaminonitrile were hydrolyzed with 6N hydrochloric acid under reflux. The resulting *N*-alkylamino acids were separated by the use of a Dowex 50 ion exchange column. A part of the *N*-benzylamino acids was recrystallized from water and ethanol. The melting points and analytical data for the *N*-benzylamino acids are shown in Table 1. The *N*-alkylamino acids were then hydrogenolyzed with palladium on charcoal. The racemic amino acids prepared by the use of benzylamine were recrystallized for elemental analyses. The results are shown in Table 2.

The syntheses of optically active amino acids by addition reaction of benzoyl cyanide to Schiff's bases which are composed of optically acitve amines were carried out in a similar way. However, in order to remove the *N*-α-alkylbenzyl group, palladium hydroxide on charcoal instead of palladium on charcoal was used. A part of the resulting amino acids were converted to their corresponding DNP derivatives. The resulting DNP derivatives were then purified by the use of a Celite column,[18] without fractionation of optical isomers.[19] These DNP derivatives were used

TABLE 2. ELEMENTAL ANALYSES OF RACEMIC AMINO ACIDS PREPARED USING BENZYLAMINE

(±)-Amino acid	Formula	Calcd (Found) C	Calcd (Found) H	Calcd (Found) N
Alanine	$C_3H_7NO_2$	40.44 (39.91)	7.92 (7.84)	15.72 (15.49)
Butyrine	$C_6H_9NO_2$	46.59 (46.84)	8.86 (8.72)	13.58 (13.46)
Valine	$C_5H_{11}NO_2$	51.26 (50.98)	9.46 (9.64)	11.96 (11.87)
Leucine	$C_6H_{13}NO_2$	54.94 (55.10)	9.99 (9.77)	10.68 (10.62)

TABLE 3. SYNTHESES OF OPTICALLY ACTIVE AMINO ACIDS

R Group of amine	CH_3CHO (Alanine) $[\alpha]_D^{25a)}$	Optical purity[b] (%)	Yield (%)	CH_3CH_2CHO (Butyrine) $[\alpha]_D^{25a)}$	Optical purity (%)	Yield (%)	$(CH_3)_2CHCHO$ (Valine) $[\alpha]_D^{25a)}$	Optical purity (%)	Yield (%)	$(CH_3)_2CHCH_2CHO$ (Leucine) $[\alpha]_D^{25a)}$	Optical purity (%)	Yield (%)
Benzyl	—	—	57	—	—	40	—	—	38	—	—	41
R(+)-Me	−33.4	23.2	46	—	—	—	—	—	—	—	—	—
S(−)-Me	+36.4	25.2	49	+36.8	37.2	35	+21.4	19.7	22	+16.2	27.1	23
S(−)-Et	+29.4	20.3	52	+32.2	32.6	33	+18.5	17.0	26	+12.3	20.3	15
S(−)-Naph	+30.2	21.0	44	+30.6	31.0	30	+42.9	39.3	24	+15.0	25.1	21

Benzyl: benzylamine; *R*(+)-Me, *R*(+)-α-methylbenzylamine; *S*(−)-Me, *S*(−)-α-methylbenzylamine; *S*(−)-Et, *S*(−)-α-ethylbenzylamine; *S*(−)-Naph, *S*(−)-α-(1-naphthyl)ethylamine.

a) Specific rotations of DNP-amino acids measured in 1N NaOH.

b) Optical purity defined as $[\alpha]_D^{25}$ obsd/$[\alpha]_D^{25}$ of the compound × 100.
DNP-*S*(+)-alanine, $[\alpha]_D^{25}$ +143.9° (1N NaOH)
DNP-*S*(+)-butyrine, $[\alpha]_D^{25}$ +98.8° (1N NaOH)
DNP-*S*(+)-valine, $[\alpha]_D^{25}$ +109.1° (1N NaOH)
DNP-*S*(+)-leucine, $[\alpha]_D^{25}$ +59.5° (1N NaOH)

c) The yields are calculated from Schiff's bases.

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to measure the optical purities of resulting amino acids. The specific rotations, optical purities, and synthetic yields of amino acids are listed in Table 3. However, DNP-leucine is difficult to crystallize and the elimination of dinitrophenol from the DNPylated reaction mixture by sublimation before celite column chromatography is probably not complete. Therefore, the specific rotations and optical purities of leucine listed in Table 3 are thought to be lower than those of the actual values. The other part of amino acids were recrystallized from water and alcohol for elemental analyses. Some of the elemental analyses of optically active amino acids prepared from *S*(−)-α-methylbenzylamine are shown in Table 4.

Table 4. Elemental analyses of optically active amino acids using *S*(−)-α-methylbenzylamine

	Formula	Calcd (Found)		
		C	H	N
S-Alanine	$C_3H_7NO_2$	40.44 (40.33)	7.92 (7.87)	15.72 (15.69)
S-Butyrine	$C_4H_9NO_2$	46.59 (46.83)	8.86 (8.81)	13.58 (13.70)
S-Valine	$C_5H_{11}NO_2$	51.62 (50.87)	9.46 (9.34)	11.96 (11.68)
S-Leucine	$C_6H_{13}NO_2$	54.94 (55.10)	9.99 (9.89)	10.68 (10.43)

The overall yield of amino acid is in a range of 20—60%. The yield of alanine is the highest; however, the yields decrease as the size of the alkyl group of the aldehyde increases. In all cases the yields of racemic α-amino acids prepared from sterically least hindered benzylamine are the highest. When *S*(−)-amine and *R*(+)-amine were used, the configurations of the resulting amino acids were (*S*)- and (*R*)- respectively. The facts agree with the results obtained in the related Strecker type asymmetric synthesis.[13-17] The optical purities are in a range of 15—39%. The effect of optically active amines on the resulting amino acids is not clear, except in the case of valine synthesis. The optical purity of (*S*)-valine prepared by the use of *S*(−)-α-(1-naphthyl)ethylamine was 39% compared with less than 20% of optical purity prepared by α-methyl- or α-ethylbenzylamine.

Experimental

All hydrogenolysis reactions were carried out by the use of Paar 3910 shaker type hydrogenation apparatus. All optical activity measurements were carried out on a JASCO-ORD-UV 5 spectropolarimeter.

The specific rotations of optically active amines were:
R(+)-α-methylbenzylamine, $[\alpha]_D^{25}+41.5°$ (benzene)
S(−)-α-methylbenzylamine, $[\alpha]_D^{25}-42.3°$ (benzene)
S(−)-α-ethylbenzylamine, $[\alpha]_D^{25}-21.0°$ (benzene)
S(−)-α-(1-naphthyl)ethylamine, $[\alpha]_D^{25}-86.5°$ (benzene)

Preparation of the Schiff's Base (VI). To the solution of benzylic amine (0.01 mol) in 15 m*l* of anhydrous benzene was added a solution of an aldehyde (0.01 mol) in 15 m*l* of benzene under ice cooling. The solution was kept in ice water for five minutes under occasional shaking. Then the solution was kept at room temperature for twenty minutes. To the mixture, 5.0 g of anhydrous sulfate was added to remove precipitated water. The benzene solution was kept for another 12 hr at room temperature. The mixture was filtered to remove sodium sulfate and the filtrate was evaporated under reduced pressure at a temperature below 45°C using a water bath. The pale yellow syrup (Schiff's base) was used for addition without further purification.

Preparation of N-*Benzoyl*-N-*alkylaminoacetonitrile (VII).* Freshly distilled benzoyl cyanide (1.30 g, 0.01 mol) in anhydrous ether (15 m*l*) was added to a solution of the Schiff's base (0.01 mol) in 15 m*l* of anhydrous ether. The reaction mixture was allowed to stand for 20 hr at room temperature. Then the ether was evaporated and the residue was used for further hydrolysis.

N-*Alkylamino Acids (VIII).* The crude *N*-benzoyl-*N*-alkyl-aminoacetonitrile (VII) was refluxed with 6N HCl (30 m*l*) for 6 hr. After the hydrolysis was over, the hydrochloric acid was removed under reduced pressure. To the residue, water (20 m) was added and the evaporation procedures were repeated 3 times to minimize the residual hydrochloric acid. The residue was dissolved in a small amount of water and was applied to a Dowex 50 column (H^+ form, 19×2.3 cm). The column was washed with water and then the column was eluted with 1.5N aqueous ammonia. The fractions containing *N*-alkylamino acid were combined and were evaporated to dryness under reduced pressure. In the *N*-benzylamino acid preparation, the residue was divided into two portions. A part was recrystallized from water and ethanol for elemental analysis and the remaining part was used for further hydrogenolysis. The melting points and elemental analyses of racemic *N*-benzylamino acids prepared by the use of benzylamine are listed in Table 1.

Amino Acids (IX). The *N*-alkylamino acid was dissolved in a mixture (60 m*l*) of water and ethanol (1:1 in volume). The solution was mixed with 0.8 g of palladium hydroxide on charcoal (in the case of *N*-benzylamino acid, 5% palladium on charcoal was used), and was hydrogenolyzed for 12 hr. After hydrogenolysis was over, the catalyst was removed by filtration. Free amino acid was obtained by evaporation of the solvent. A part of the amino acid was recrystallized from water and ethanol for elemental analysis. The elemental analyses of racemic amino acid prepared by the use of benzylamine are listed in Table 2. The elemental analyses of optically active amino acid prepared from *S*(−)-α-methylbenzylamine are shown in Table 4. The optically active amino acids were converted to DNP-amino acids in the usual way,[20] and the resulting DNP-amino acids were purified by the use of a Celite column treated with pH 7 citrate–phosphate buffer.[18] The specific rotations, optical purities, and overall yields are shown in Table 3.

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