Sterically Controlled Syntheses of Optically Active Organic Compounds. XVIII. Asymmetric Syntheses of Amino Acids by Addition of Hydrogen Cyanide to the Schiff Bases[1]

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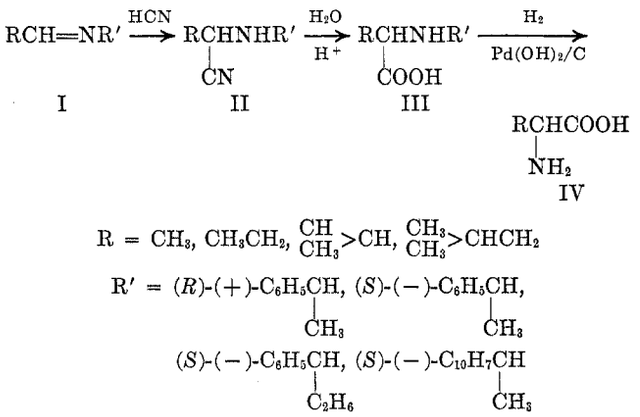
Addition reactions of hydrogen cyanide to Schiff bases which were prepared from several aliphatic aldehydes and optically active benzylic amines were studied. The addition products were hydrolyzed and hydrogenolyzed to form optically active amino acids. The synthetic yields of amino acids were in a range of 9–58% and the optical purities of amino acids without fractionation of optical isomers were in a range of 22–58%. When (*R*)-α-alkylbenzylamines were used, (*R*)-amino acids were obtained. The fractionation of optical isomers during isolation and purification was examined.

Partially optically active *N*-alkyl-α-aminopropionitrile was prepared by the Strecker reaction from optically active α-methylbenzylamine, acetaldehyde and hydrogen cyanide,[2] or from the same amine with racemic lactonitrile.[3] The *N*-α-methylbenzylaminoacetonitrile was hydrolyzed and hydrogenolyzed to form optically active alanine.[2,3] From the reaction mixture, highly optically active alanine (optical purity 89–98%) was isolated by crystallization in which fractionation of optical isomers would take place.[4]

Addition reactions to the carbon–nitrogen double bonds have been studied.[5,6] Carbon–nitrogen double bonds react with hydrogen cyanide to form α-amino nitriles.[7–15] Hydrolysis of the amino nitriles yielded α-amino acids.

Recently, Patel and Worsley[16] reported the asymmetric synthesis of several α-amino acids (mostly unnatural) by addition of hydrogen cyanide to the carbon–nitrogen double bond of Schiff bases that were 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 purity could have resulted from fractionation which occurred during the crystallization and the washing procedure employed in the synthesis.

In this investigation, the addition reactions of hydrogen cyanide to azomethine compounds (I) which were prepared from various optically active benzylic amines and aliphatic aldehydes were studied in order to (1) examine the fractionation problem in the previous study,[16] (2) examine the effect of optically active benzylic amines on the optical purity of the synthesized amino acids, and (3) synthesize natural amino acids. The amines used were (*R*)-(+)- and (*S*)-(−)-α-methylbenzylamine, (*R*)-(+)-α-ethylbenzylamine, and (*R*)-(+)-α-(1-naphthyl)ethylamine. The aldehydes



used were acetaldehyde, propionaldehyde, isobutyraldehyde, and isovaleraldehyde, which resulted in the formation, respectively, of the natural amino acids, alanine, butyrine, valine, and leucine.

The addition reaction of hydrogen cyanide to the Schiff bases was carried out in absolute ethanol for 20 hr at room temperature; however, the addition of hydrogen cyanide to the Schiff base was carried out at −10°. The reaction products that contain *N*-alkylaminonitriles (II) were hydrolyzed by refluxing in 6 *N* hydrochloric acid. The resulting *N*-alkylamino acids (III) were hydrogenolyzed with palladium hydroxide on charcoal in order to remove the *N*-α-alkylbenzyl group. The resulting amino acids (IV) were converted to their corresponding DNP derivatives by treatment with 2,4-dinitrofluorobenzene. The DNP amino acids were purified by the use of Celite column chromatography[17] without fractionation of optical isomers.[18] These DNP derivatives were used to measure the optical purities of the resulting amino acids. The overall yields, specific rotations, and optical purities of alanine, butyrine, valine, and leucine that were synthesized using various optically active amines are listed in Table I.

The overall yield of amino acids is in a range of 19–58%. Valine, which is the most sterically hindered, had the lowest yield, and alanine, which is the least sterically hindered, had the highest yield. The effect

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TABLE I

ASYMMETRIC SYNTHESES OF AMINO ACIDS BY ADDITION OF HYDROGEN CYANIDE TO THE SCHIFF BASES

Aldehyde		CH_3CHO			CH_3CH_2CHO		
Reaction	Amine[a]	DNP-Ala[b] $[\alpha]^{25}D$ (c)	Optical purity[c]	Overall yield,[d] %	DNP-But[b] $[\alpha]^{25}D$ (c)	Optical purity[c]	Overall yield,[d] %
1a	(*R*)-(+)-Me	−56.8 (2.0)	40	54	−47.5 (1.7)	48	49
1b		−64.1 (1.8)	45	40	−55.0 (1.9)	56	37
1c		−116.8 (1.6)	81	25	−93.5 (1.6)	95	14
1d		−9.5[e] (2.7)	95[e]	17	−14.8[e] (1.8)	100[e]	14
2	(*S*)-(−)-Me	+58.1 (2.0)	41	58	+48.9 (1.8)	49	43
3	(*R*)-(+)-Et	−76.0 (1.7)	53	52	−54.8 (1.6)	55	41
4	(*R*)-(+)-Naph	−53.4 (1.9)	37	54	−52.6 (1.5)	53	45

$(CH_3)_2CHCHO$			$(CH_3)_2CHCH_2CHO$		
DNP-Val[b] $[\alpha]^{25}D$ (c)	Optical purity[c]	Overall yield,[d] %	DNP-Leu[b] $[\alpha]^{25}D$ (c)	Optical purity[c]	Overall yield,[d] %
−34.2 (1.4)	31	21	−14.1 (2.3)	24	40
−52.2 (0.7)	48	12	−20.1 (2.3)	34	23
−66.8 (1.2)	61	9	−24.3 (2.6)	41	
−16.3[e] (1.7)	74[e]	10	−9.0[e] (2.0)	78[e]	14
+32.2 (1.2)	30	19	+13.8 (2.9)	23	37
−52.3 (1.5)	48	19	−17.5 (4.4)	30	35
−48.4 (1.5)	44	22	−13.0 (4.9)	22	34

[a] (*R*)-(+)-Me, (*R*)-(+)-α-methylbenzylamine; (*S*)-(−)-Me, (*S*)-(−)-α-methylbenzylamine; (*R*)-(+)-Et, (*R*)-(+)-α-ethylbenzylamine; (*R*)-(+)-Naph, (*R*)-(+)-α-(1-naphthyl)ethylamine. [b] These specific rotations of DNP amino acids were measured in 1 *N* NaOH. [c] Optical purity defined as $[\alpha]D$ obsd/$[\alpha]D$ of the compound × 100. DNP-(*S*)-(+)-alanine, $[\alpha]D$ +143.9° (1 *N* NaOH); DNP-(*S*)-(+)-butyrine, $[\alpha]D$ +98.8° (1 *N* NaOH); DNP-(*S*)-(+)-valine, $[\alpha]D$ +109.1° (1 *N* NaOH); DNP-(*S*)-(+)-leucine, $[\alpha]D$ +59.5° (1 *N* NaOH). [d] The yields are calculated from aldehydes. [e] Specific rotations and optical purities are measured as amino acid hydrochlorides.

TABLE II

ELEMENTAL ANALYSES OF AMINO ACIDS AND *N*-ALKYLAMINO ACIDS

			Calcd, %			Found, %		
Compd	Mp, °C	Formula	C	H	N	C	H	N
N-R-Ala[a]	273–276 (sublime)	$C_{11}H_{15}NO_2$	68.37	7.82	7.25	68.49	7.95	7.17
N-R-But[a]	247–250 (sublime)	$C_{12}H_{19}NO_2$	69.54	8.27	6.76	69.22	8.40	6.65
N-R-Val[a]	265–270 (sublime)	$C_{13}H_{19}NO_2$	70.56	8.65	6.33	70.21	8.79	6.34
N-R-Leu[a]	255–258 (sublime)	$C_{14}H_{21}NO_2$	71.46	8.99	5.95	71.53	9.12	6.05
Ala		$C_3H_9NO_2$	40.44	7.92	15.72	40.56	7.88	15.78
But		$C_4H_9NO_2$	46.59	8.80	13.58	46.94	8.80	13.66
Val		$C_5H_{11}NO_2$	51.26	9.46	11.96	51.06	9.42	11.98
Leu		$C_6H_{13}NO_2$	54.94	9.99	10.68	54.72	9.95	10.63

[a] R: (*R*)-(+)-α-methylbenzyl.

of various optically active amines on the overall yield is not clear. The effect of amines on the optical purities of amino acid is also not large; however, the optical purities of amino acids prepared by the use of (*R*)-(+)-α-ethylbenzylamine are always the largest. This result agrees with the data that were obtained by other Strecker-type syntheses of amino acids using the same amines under similar conditions.[4] DNP-leucine is difficult to crystallize and the elimination of 2,4-dinitrophenol from the DNP-ylated reaction mixture by sublimation before Celite column chromatography is probably not complete. Therefore, the specific rotations and optical purities of leucine (measured as DNP-leucine) listed in Table I could be thought to be lower than those of the actual values. Elemental analyses of some of the *N*-alkylamino acids and also alanine, butyrine, valine, and leucine are shown in Table II.

In reaction series 1a, Table I, partially optically active alanine, butyrine, valine, and leucine were

prepared by the use of (*R*)-(+)-α-methylbenzylamine and the optical purities of these DNP amino acids were measured without fractionation of optical isomers as in the previous studies.[18] In reaction series 1b, 1c, and 1d, Table I, several washing and isolation procedures that were used by Patel and Worsley[16] were examined.

In reaction 1b, the isolated compound III was washed with absolute alcohol after isolation by the use of a Dowex 50 column. It was found that some of the optically active diastereomeric mixture (III) dissolved easily in absolute alcohol, especially for *N*-alkylvaline and *N*-alkylleucine. The alcohol-washed III was hydrogenolyzed and the optical purities of the resulting amino acids were measured with the DNP-ylation technique without further fractionation of optical isomers. Therefore, the increase of optical purities in reaction 1b compared with 1a in Table I can be attributed to the washing of the isolated diastereomeric mixtures.

In reaction 1c, the diastereomeric mixture III was isolated after adjusting the pH to 6 by the addition of alcohol, instead of by using ion-exchange resin. The isolated compounds were then hydrogenolyzed and the optical purities of amino acids were measured without fractionation. The increase of optical purity in reaction 1c compared with 1a in Table I can be attributed to fractionation during crystallization in the isolation procedure.

In reaction 1d, amino acids which were obtained by the hydrogenolysis of reaction 1c were dissolved in 1 *N* hydrochloric acid. After the solution was evaporated to dryness, the residual amino acid hydrochlorides were dissolved in a small amount of absolute ethanol and the amino acid hydrochlorides were precipitated by addition of ether. The optical purities of amino acid hydrochlorides were measured directly without converting them to DNP derivatives. Therefore, the increase of optical purity of reaction 1d compared with 1c can be attributed to fractionation during crystallization of the amino acid hydrochlorides.

These artificially designed fractionations of optically active isomers by washing and crystallization of the diastereomeric mixture and by crystallization of the partially optically active amino acid hydrochlorides indicate strongly that the high optical purities obtained in the earlier study[16] are due to the fractionation during the isolation and purification procedures.[18a]

Experimental Section

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

The specific rotations of optically active amines follow: (*R*)-(+)-α-methylbenzylamine, $[\alpha]^{25}D$ −39.0° (*c* 5, benzene); (*S*)-(−)-α-methylbenzylamine, $[\alpha]^{25}D$ −38.5° (*c* 5, benzene); (*S*)-(−)-α-ethylbenzylamine, $[\alpha]^{25}D$ +21.1° (*c* 6, benzene); (*R*)-(−)-α-(1-naphthyl)ethylamine, $[\alpha]^{25}D$ +91.0° (*c* 7, benzene).

Preparation of the Schiff Base I.—To the solution of benzylic amine (0.01 mol) in 15 ml of anhydrous benzene was added a solution of an aldehyde (0.01 mol) in 15 ml of benzene under ice cooling. The solution was kept in ice water for 5 min with occasional shaking. Then the solution was kept at room temperature for 20 min. To the mixture, 5.0 g of anhydrous sodium 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° using a water bath. The pale yellow syrup (Schiff base) was used in the addition reactions.

α-Aminonitriles (II).—The Schiff base I was dissolved in 20 ml of absolute ethanol. The solution was chilled to −10° and then 2 ml (0.05 mol) of liquid hydrogen cyanide was added. The reaction mixture was shaken to mix the reactants homogeneously. Then the container was sealed and the reaction mixture was allowed to stand at room temperature for 20 hr. The reaction mixture was colorless to pale yellow after standing. After the reaction was over, excess hydrogen cyanide and ethanol were removed under reduced pressure using a sodium hydroxide trap. The residual syrup (aminonitrile, II) was processed further by hydrolysis.

***N*-Alkylamino Acids (III).**—The α-aminonitrile II was refluxed with 20 ml of 6 *N* hydrochloric acid for 12 hr. The hydrolyzate was extracted with ether to remove colored ether-soluble material. The hydrochloric acid was evaporated to dryness under reduced pressure. Absolute ethanol (20 ml) was added to the residue, the solution was kept at 0° for 3 hr, and the solution was filtered to remove ammonium chloride. The ethanol was evaporated under reduced pressure. The residue was dissolved in a small amount of water, and the solution was applied to a Dowex 50 column (H^+ form, 1.9 × 23 cm) and was eluted with 1.5 *N* aqueous ammonia after water washing. The fractions containing the amino acid were combined and the solution was evaporated under reduced pressure. Half of the *N*-alkylalanine, *N*-alkylbutyrine, *N*-alkylvaline, and *N*-alkylleucine, where the *N*-alkyl group is an (*R*)-(+)-α-methylbenzyl group, was recrystallized from ethanol and water for elemental analysis. The results are shown in Table II. Half of the other *N*-alkylamino acids were hydrogenolyzed without isolation to avoid fractionation of optical isomers.

Optically Active Amino Acid IV.—*N*-Alkylamino acid III was dissolved in a mixture of ethanol and water (70 ml, 1:1), and the solution was hydrogenolyzed by the use of palladium hydroxide on charcoal (0.5 g) for 12 hr. After the reaction was over, a part of the amino acid was converted to DNP amino acid in the usual manner.[19] The resulting DNP amino acid was purified and isolated by the use of a Celite column treated with a pH 7 citrate–phosphate buffer.[17] The DNP amino acid was used for measurement of optical purity of amino acid. The other part of the amino acid was recrystallized from water and ethanol for elemental analysis. The elemental analyses of alanine, butyrine, valine, and leucine, which were prepared by the use of (*R*)-(+)-α-methylbenzylamine, are shown in Table II.

Fractionation of Optical Isomers during the Isolation and Purification Processes. Reaction 1b.—After acid hydrolysis, the *N*-alkylamino acid III was isolated by the use of a Dowex 50 column as described earlier. The *N*-alkylamino acids III (a diastereomeric mixture) were washed with varying amounts of absolute alcohol (*N*-alkylalanine, 15 ml; *N*-alkylbutyrine, 15 ml; *N*-alkylvaline, 3 ml; *N*-alkylleucine, 3 ml). *N*-Alkylvaline and *N*-alkylleucine are rather soluble in absolute alcohol and only 3 ml of ethanol was used for washing. The alcohol-washed *N*-alkylamino acids were dissolved in an ethanol–water mixture (1:1) and hydrogenolyzed. The optical purities were measured as DNP derivatives after purification using Celite column chromatography.

Reaction 1c.—After acid hydrolysis of II, the hydrochloric acid was evaporated under reduced pressure. The residue was dissolved in 7–16 ml of water and the pH was adjusted to 6 with pyridine. To this solution, an equal volume of absolute ethanol was added to precipitate the *N*-alkylamino acid III. Crystallized III was hydrogenolyzed and DNP-ylated to measure the optical purity of amino acid as described above.

Reaction 1d.—The amino acid IV, which was obtained by the method described in reaction 1c, was dissolved in 10 ml of 1 *N* hydrochloric acid, and the solution was evaporated to dryness. The residue was dissolved in 1.5–3 ml of absolute ethanol. To this was added 3–8 ml of ether to precipitate amino acid hydrochloride. The optical purities were measured as amino acid

(18a) NOTE ADDED IN PROOF.—Recent study showed that the optical purity of amino acid prepared by the method described in ref 16 was 60% by using nmr technique: J. C. Fiaud and A. Horeau, *Tetrahedron Lett.*, 2565 (1971).

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hydrochloride instead of as DNP derivatives. The results of reactions 1b, 1c, and 1d are shown in Table I.

Registry No.—I (R = Me, R′ = (*R*)-(+)-Me), 37696-13-2; I (R = Me, R′ = (*S*)-(−)-Me), 37696-14-3; I (R = Me, R′ = (*R*)-(+)-Et), 37696-15-4; I (R = Me, R′ = (*R*)-(+)-Naph), 37696-16-5; I (R = Et, R′ = (*R*)-(+)-Me), 37696-17-6; I (R = Et, R′ = (*S*)-(−)-Me), 37696-18-7; I (R = Et, R′ = (*R*)-(+)-Et, 37696-19-8; I (R = Et, R′ = (*R*)-(+)-Naph), 37696-20-1; I (R = *i*-Pr, R′ = (*R*)-(+)-Me), 6397-96-2; I (R = *i*-Pr, R′ = (*S*)-(−)-Me), 6397-97-3; I (R = *i*-Pr, R′ = (*R*)-(+)-Et), 37696-23-4; I (R = *i*-Pr, R′ = (*R*)-(+)-Naph), 37696-24-5; I (R = *i*-Bu, R′ = (*R*)-(+)-Me), 27482-979; I (R = *i*-Bu, R′ = (*S*)-(−)-Me), 27482-980; I (R = *i*-Bu, R′ = (*R*)-(+)-Et), 37696-27-8; I (R = *i*-Bu, R′ = (*R*)-(+)-Naph), 37696-28-9; *N*-(*R*)-(+)-Me-Ala (DL), 37696-29-0; *N*-(*R*)-(−)-Me-But (DL), 37696-30-3; *N*-(*R*)-(+)-Me-Val (DL), 37696-31-4; *N*-(*R*)-(+)-Me-Leu (DL), 37696-32-5; D-Ala, 338-69-2; D-But, 2623-91-8; D-Val, 640-68-6; D-Leu, 328-38-1; D-Ala (DNP), 10580-45-7; D-But (DNP), 6367-34-6; D-Val (DNP), 37696-35-8; D-Leu (DNP), 37696-36-9.

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Structure and Conformation of Chalcone Photodimers and Related Compounds

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Based on combined evidence from various techniques, we report here the configurational assignments and the conformational preferences of the two chalcone (benzalacetophenone) photodimers. Mass spectra and nmr data have provided much of the evidence for the configurational assignments, while dipole moment data and conformational energy estimates have been used in the conformational work. Detailed analysis of mass and nmr spectra has allowed to assign the β-truxinic structure to the low-melting (mp 126°) photodimer and the α-truxillic structure to the high-melting (mp 226°) photodimer. These results modify previous reports which assigned the δ-truxinic structure to the low-melting isomer. The conformational properties of these molecules have been investigated by comparing the experimental dipole moments with contour maps of calculated dipole moments as a function of the internal rotation angles, and with conformational energy maps. Our results show that these structurally crowded molecules experience drastic restrictions of the conformational space available, so that they exist in well-defined, thermodynamically preferred conformations.

Owing to the widespread activity in the field of photodimerization reactions, structural studies on compounds containing cyclobutane rings recently attracted wide interest. Furthermore, photodimerization of unsaturated compounds often yields crowded cyclobutanes which may possess interesting conformational properties.

In the following, we report a study of the structure and conformational preferences of the two chalcone photodimers. Although the above compounds have been long known,[1] their stereochemistry has not been worked out in detail and we have combined several techniques to investigate the various aspect of the problem.

Evidence for a correct configurational assignment is here obtained by combining the mass and nmr data relative to the two photodimers, and comparing these data with those relative to a number of related compounds of known structure. The (novel) chlorinated derivatives of the two chalcone photodimers proved useful both in the elucidation of the mass spectra and in the interpretation of the dipole moment data.

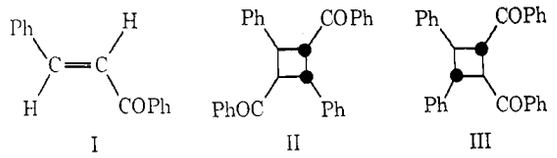
Dipole moment data and conformational energy estimates have been used to detect the conformational preferences of the photodimers.

Dipole moment data, being conformation dependent, may prove very useful in conformational studies but often do not provide unequivocal information, since different conformations may be calculated to have the same dipole moment value.[2] We have therefore found it desirable to generate a conformational energy contour map for each compound and to show that the calculated dipole moment corresponding to the energetically allowed region (preferred conformation) fits the experimental dipole moment.

Structural Assignments

Irradiation of chalcone (I) is known to produce a dimer the structure of which depends on the reaction phase employed.[1]

The high-melting (mp 226°) isomer, produced by solid-state irradiation, has been assigned[3] a structure II, while the low-melting (mp 126°) isomer, produced in solution, has been assigned[3] a structure III.



I II III

These assignments, however, were based on a complex series of chemical reactions in which the possibility of isomerizations was not eliminated, so that they appear tentative[4] at best.

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