Sterically Controlled Syntheses of Optically Active Organic Compounds. XX. Synthesis of Optically Active Alanine from α-Bromopropionamides[1]

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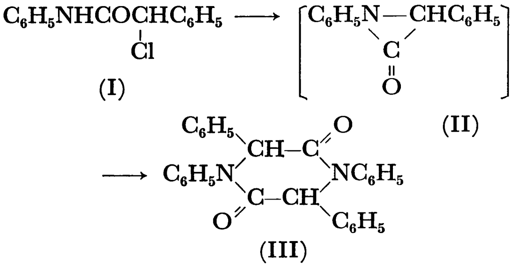
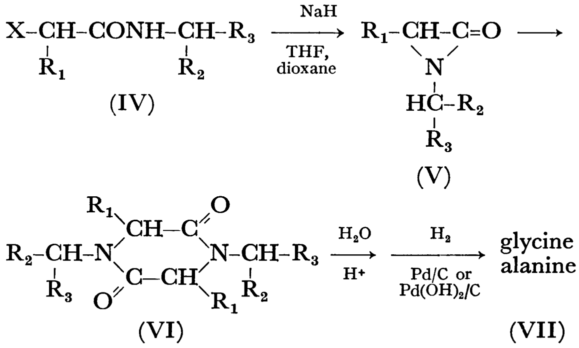
The treatment of *N*-benzylchloroacetamide with sodium hydride resulted in the formation of *N,N'*-dibenzyldiketopiperazine which was converted to glycine after hydrolysis and hydrogenolysis. In a similar way, *N*-alkyl-α-bromopropionamides, in which the alkyl groups were chiral, were treated with sodium hydride and optically active alanine was obtained after hydrolysis and hydrogenolysis. When an optically active (*S*)-(−)- or (*R*)-(+)-α-methylbenzyl group was used as a chiral center, the optical activity of alanine was very low. When (*S*)-(−)-α-ethylbenzylamine was used, optically active (*S*)-alanine (optical purity 6—25%) was obtained. The use of (*S*)-(−)-α-(1-naphthyl)ethylamine resulted in the formation of (*R*)-alanine (opposite configuration, optical purity 23—27%). The overall yield of optically active alanine is in the range 11—36%.

It has been reported by Sarel and Ben-Shoshan that the α-chloropropionanilide was converted to *N*-phenyl-α-lactam by the action of sodium amide in liquid ammonia.[2] Sarel and Greenberger further reported[3] the chemical reaction of sodium hydride with α-chloro-α-phenylacetanilide (I) in dry benzene. The major product of this reaction was 1,3,4,6-tetraphenylpiperazine-2,5-dione (III), which could be converted to *N*-phenyl phenylglycine upon hydrolysis. In this reaction it was assumed that the three membered reactive intermediate (α-lactam) (II) dimerized to form a more stable six-membered ring product (III). In the inert solvent, only the dimerization reaction could take place to form the diketopiperazine derivative. Later it was reported that the postulated α-lactam and its corresponding diketopiperazine were isolated.[4] However, Sheehan and Frankenfeld[5] established that α-lactam was not found among the final products of the reaction of α-chloroanilides with sodium hydride. Baumgarten *et al.*[6] confirmed the existence of α-lactam spectroscopically. Since then, several α-lactam formations and their chemistry have been studied.[7-17]



In this paper, the syntheses of glycine and alanine from α-haloacylamides were examined. The α-haloacylamides were prepared from several benzylic amines by acylation with α-chloroacetyl anhydride or with α-bromopropionyl bromide. The benzylic amines used were benzylamine, (±)-α-methylbenzylamine, (*R*)-(+)-α-methylbenzylamine, (*S*)-(−)-α-methylbenzylamine, (*S*)-(−)-α-ethylbenzylamine, and (*S*)-(−)-α-(1-naphthyl)-ethylamine.

In the glycine synthesis, *N*-benzyl-α-chloroacetamide (IV, X=Cl, R_1=H, R_2=H, R_3=phenyl) was treated with sodium hydride in anhydrous tetrahydrofuran at varying temperatures (0, 25, and 50°C). After evaporation of the solvent and recrystallization of the residual material, *N,N'*-dibenzylpiperazine-2,5-dione (VI) was isolated. The VI was hydrolyzed and hydrogenolyzed to form glycine (overall yield 17 to 52%).



X: Cl, Br
R_1: H, Me
R_2: H, Me, Et
R_3: Phenyl, Naphthyl

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TABLE 1. *N*-ALKYL-α-BROMOPROPIONAMIDE

$\mathrm{CH_3\text{-}\underset{Br}{CH}\text{-}CONHR}$ R[a]	Formula	$[\alpha]^{25}_{D}$ (THF)	Mp, °C	Calcd %			Found %		
				C	H	N	C	H	N
(±)-Me	$C_{11}H_{14}NOBr$	—	129—130	51.58	5.51	5.47	51.59	5.64	5.58
(*R*)-(+)-Me	$C_{11}H_{14}NOBr$	+59.8	108—109	51.58	5.51	5.47	51.23	5.65	5.54
(*S*)-(−)-Me	$C_{11}H_{14}NOBr$	−59.5	108—109	51.58	5.51	5.47	51.49	5.71	5.38
(*S*)-(−)-Et	$C_{12}H_{16}NOBr$	−66.8	77—79	53.35	5.97	5.18	53.42	6.16	5.16
(*S*)-(−)-Naph	$C_{15}H_{16}NOBr$	−20.4	176—177	58.64	5.27	4.57	58.70	5.46	4.67

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

TABLE 2. SYNTHESES OF GLYCINE AND ALANINE FROM α-HALOACYLAMIDES

	$\mathrm{R^{*}NHCO\underset{X}{C}HR}$ R*[a]	R	X	Reaction conditions Solvent	Temp (°C)	Time (hr)	Synthesized amino acid Config.	DNP-Alanine[b] $[\alpha]^{25}_{D}$ (c=1.6∼1.9)	Opt. purity[c] (%)	Yield[d] (%)
1	Benzyl	H	Cl	Anhy THF	0	12	—	—	—	17
2	Benzyl	H	Cl	Anhy THF	25	12	—	—	—	20
3	Benzyl	H	Cl	Anhy THF	50	8	—	—	—	52
4	(±)-Me	CH_3	Br	Anhy Dioxane	25	12	—	—	—	8
5	(±)-Me	CH_3	Br	Anhy Dioxane	25	36	—	—	—	38
6	(±)-Me	CH_3	Br	Anhy Dioxane	25	72	—	—	—	23
7	(*R*)-(+)-Me	CH_3	Br	Anhy THF	0	84	±	0	—	29
8	(*S*)-(−)-Me	CH_3	Br	Anhy THF	0	84	*R*	−1.9	1.3	21
9	(*S*)-(−)-Et	CH_3	Br	Anhy THF	0	84	*S*	+9.2	6.4	11
10	(*S*)-(−)-Naph	CH_3	Br	Anhy THF	0	84	*R*	−39.2	27.2	14
11	(*R*)-(+)-Me	CH_3	Br	Anhy THF	25	36	*R*	−2.4	1.7	30
12	(*R*)-(+)-Me	CH_3	Br	Anhy THF	25	72	*R*	−1.8	1.2	20
13	(*S*)-(−)-Me	CH_3	Br	Anhy THF	25	36	*S*	+2.6	1.8	20
14	(*S*)-(−)-Et	CH_3	Br	Anhy THF	25	36	*S*	+35.6	24.8	17
15	(*S*)-(−)-Naph	CH_3	Br	Anhy THF	25	12	*R*	−33.0	32.0	18
16	(*S*)-(−)-Naph	CH_3	Br	Anhy THF	25	36	*R*	−36.0	25.2	14
17	(*S*)-(−)-Naph	CH_3	Br	Anhy THF	25	72	*R*	−37.9	26.4	17
18	(*S*)-(−)-Me	CH_3	Br	Anhy THF	50	5	*S*	+3.6	2.5	27
19	(*S*)-(−)-Et	CH_3	Br	Anhy THF	50	5	*S*	+31.3	21.7	24
20	(*S*)-(−)-Naph	CH_3	Br	Anhy THF	50	5	*R*	−34.3	23.8	27

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

b) Specific rotation of DNP-anlanine was measured in 1M NaOH.

c) Defined as $[\alpha]_D$ obsd/$[\alpha]_D$ of the compound ×100. DNP-(*S*)-(+)-Alanine, $[\alpha]^{25}_{D}$ +143.9° (1M NaOH).

d) The yields are calculated from *N*-alkyl-α-haloacidoamide by using automatic amino acid analyzer.

In a similar way, several α-bromopropionamides (IV, X=Br, R_1=CH_3, R_2=Me or Et, R_3=phenyl or naphthyl) were prepared from racemic α-bromopropionyl bromide with racemic and also optically active α-alkylbenzylamines and optically active α-(1-naphthyl)ethylamine. Table 1 shows the physical properties and elemental analyses of *N*-alkyl-α-bromopropionamides prepared. At varying temperatures, the compounds (IV) were treated with sodium hydride in dioxane as in the synthesis of glycine. After hydrolysis and hydrogenolysis of the reaction products, alanine was obtained in 11 to 36% yield. The reaction conditions, configurations, optical purities, and yields of alanine are summarized in Table 2.

As shown in Table 1, *N*-α-methylbenzyl-β-bromopropionamides were prepared using (*S*)-(−)-α-methylbenzylamine and (*R*)-(+)-α-methylbenzylamine. The melting points of these amides are identical and the magnitude of specific rotations are the same (the signs of rotation are opposite each other). However, this might not mean that the configurations of α-bromopropionyl residue of the prepared amides are racemic. It could be possible that the fractionation took place during amide formation, isolation, and purification. However, from the results shown in Table 2, the possible fractionation of the diastereomeric starting material seems not great.

The reactions were carried out at 0, 25, and 50°C. The yields of optically active alanine at these temperatures are not much different. The optical purities of alanine by the use of α-methylbenzylamine are usually low (0—2.5%) at all temperatures. The optical purity of alanine prepared using (*S*)-(−)-α-ethylbenzylamine at 0°C is rather low (6%); however, it increased considerably at higher temperatures (25% at 25°C, 22% at 50°C). The optical purities of alanine prepared with (*S*)-(−)-α-(1-naphthyl)ethylamine are rather high at all temperatures (24—27%) and the configuration of alanine is opposite to that prepared with (*S*)-(−)-α-ethylbenzylamine.

As shown in Table 2, the yields and optical purities of the resulting optically active alanine depending on the reaction time do not show a clear relation with the reaction time. This suggests that the reactions do not follow a simple kinetic resolution type mechanism.

In this experiment, the resulting partially optically active alanine was isolated by the use of an ion exchange resin and the resulting crude alanine was converted to DNP-alanine. The partially optically active DNP-alanine was purified by the use of celite column chromatography[18] without fractionation of optical isomers.[19]

Experimental

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, $[\alpha]$– −86.5° (benzene)

Hydrogenolysis was carried out using the Parr 3910 shaker type hydrogenation apparatus. The accuracy of reaction temperatures is about ±1°C. All optical activity measurements were carried out on the JASCO ORD-CD-UV 5 spectropolarimeter.

N-*Benzylchloroacetamide (IV, X=Cl, R_1=H, R_2=H, R_3=phenyl).* Benzylamine, 10.7 g (0.10 mol) and monochloroacetic anhydride, 17.1 g (0.10 mol), were dissolved in 200 ml of dry benzene and the solution was refluxed gently for 3 hr. After the reaction was over, the benzene solution was washed with 100 ml each of 1 M hydrochloric acid, 7% sodium hydrogen carbonate, and water. The benzene solution was dried with anhydrous sodium sulfate and the benzene was removed under reduced pressure. The residual material was recrystallized from 95% ethanol, yield 14.2 g (77%) mp 92—93°C.

Found: C, 58.68; H, 5.41; N, 7.30%. Calcd for $C_9H_{10}NOCl$: C, 58.86; H, 5.49; N, 7.63%.

N,N′-*Dibenzylpiperazinedione (VI, R_1=H, R_2=H, R_3=phenyl).* Sodium hydride (60%, 0.4 g, 0.01 mol) was suspended in 50 ml of anhydrous tetrahydrofuran (THF). To this was added slowly a solution of 1.84 g (0.01 mol) of IV in 30 ml of anhydrous THF during a period of 2 hr under cooling with ice water. After the addition was over, the solution was kept at room temperature under agitation for an additional 12 hr. After the reaction was over, precipitated sodium chloride was removed by filtration. The filtrate was divided equally into two portions. One portion was evaporated to dryness and the residue was recrystallized from ethanol, yield of VI, 0.23 g (yield 32% from IV), mp 178—180°C.

Found: C, 73.52; H, 6.21; N, 9.32%. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52%.

The other portion of the filtrate was evaporated to dryness under reduced pressure, and the residue was refluxed with 20 ml of 6 M HCl for 6 hr. After the hydrolysis was over, hydrochloric acid was removed under reduced pressure and the residue was applied to a Dowex 50 column (H^+ form, 19×23 cm) and *N*-benzylglycine was eluted with 1M aqueous ammonia after washing with water. The fractions containing *N*-benzylglycine were combined and evaporated. The residue was dissolved in ethanol–water mixture (1 : 1 in volume) and was hydrogenolyzed by the use of 5% palladium on charcoal. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure. The yield of glycine was measured by automatic amino acid analyzer after appropriate dilution, yield 17.3% from I. The glycine was recrystallized from water and ethanol for elemental analysis (Found: C, 31.74; H, 6.78; N, 18.63%).

N-*(+)-α-Methylbenzyl-(±)-α-bromopropionamide (IV, X=Br, R_1=Me, R_2=Me, R_3=Phenyl).* The solution of (±)-α-methylbenzylamine, 12.1 g (0.1 mol), was added slowly to the solution of (±)-α-bromopropionylbromide, 10.8 g (0.05 mol), in 20 ml of benzene over a period of 1 hr under cooling with ice water. The racemic α-methylbenzylamine hydrochloride was crystallized out during the reaction. The reaction mixture was stirred for 2 hr at room temperature. The precipitated compounds were filtered and washed with benzene (60 ml) to remove amide. The benzene solution was washed with 50 ml each of 1 M hydrochloric acid, 5% sodium hydrogen carbonate, and then with water. The benzene solution was dried by anhydrous sodium sulfate. After the sodium sulfate was removed by filtration, the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from 95% ethanol, yield 7.8 g (61%), mp 129—130°C.

Other amides were prepared in a similar way. The physical properties and elemental analyses of these α-bromopropionamides are summarized in Table 3.

*(*S*)-Alanine (VII) from* N-*Alkyl-α-bromopropionamide (IV, X=Br, R_1=Me, R_2=Me, R_3=phenyl).* The solution of *N*-(*S*)-(−)-α-methylbenzyl-α-bromopropionamide (IV), 1.3 g (0.005 mol), in anhydrous dioxane (20 ml) was added slowly to a suspension of sodium hydride (60%, 0.2 g, 0.005 mol) in anhydrous dioxane (20 ml) during a period of 1 hr at room temperature. After the addition was over, the reaction mixture was stirred at room temperature for another 36 hr.

TABLE 3. *N*-ALKYL-α-BROMOPROPIONAMIDE

R	Mp, °C	$[\alpha]_D^{25}$ in THF	Formula	Calcd %			Found %		
				C	H	N	C	H	N
(±)-Me	129—130	—	$C_{11}H_{14}NOBr$	51.58	5.51	5.47	51.59	5.64	5.58
(*R*)-(+)-Me	108—109	+59.8	$C_{11}H_{14}NOBr$	51.58	5.51	5.47	51.23	5.65	5.54
(*S*)-(−)-Me	108—109	−59.5	$C_{11}H_{14}NOBr$	51.58	5.51	5.47	51.49	5.71	5.38
(*S*)-(−)-Et	77—79	−66.8	$C_{12}H_{16}NOBr$	53.35	5.97	5.18	53.42	6.16	5.16
(*S*)-(−)-Naph	176—177	−20.4	$C_{15}H_{16}NOBr$	58.85	5.27	4.57	58.70	5.46	4.67

(+)-Me, (+)-α-methylbenzyl;(*R*)-(+)-Me, (*R*)-(+)-α-methylbenzyl; (*S*)-(−)-Me, (*S*)-(−)-α-methylbenzyl; (*S*)-(−)-Et, (*S*)-(−)-α-ethylbenzyl; (*S*)-(−)-Naph, (*S*)-(−)-α-(1-naphthyl)ethyl.

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The precipitated sodium bromide was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was refluxed with 30 ml of 6 M HCl for 6 hr. The hydrolyzate was extracted with ether and the hydrochloric acid was evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of water and was applied on a Dowex 50 column (H^+ form). The column was eluted with 1 M aqueous ammonia after washing the column with water. The fractions containing *N*-alkylalanine were combined and evaporated to dryness. The residual *N*-alkylalanine was dissolved in water and alcohol mixture (1: 1) and was hydrogenolyzed with 0.5 g $Pd(OH)_2/C$ for 12 hr. After the hydrogenolysis was complete, the catalyst was removed by filtration. Part of the solution was diluted in the proper way and was analyzed by an automatic amino acid analyzer to determine the yield of alanine, 19.7%. The other part of the alanine solution was evaporated to dryness and the residue was recrystallized from water and ethanol for elemental analysis of alanine (Found: C, 40.03; H, 7.84; N, 15.34%).

The other part of the alanine solution was converted to its DNP-derivative in the usual manner. The resulting DNP-alanine was purified by the use of a celite column treated with pH 7 citrate-phosphate buffer.[18] The yields, specific rotations, and optical purities of alanine preparations are summarized in Table 2.

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