Approach to the Use of Benzylpenicillinacylase for Configurational Correlations of Amino Compounds. 2.[1] Hydrolysis of *N*-(*p*-Aminophenylacetyl) Derivatives of Some Chiral Primary Amines

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A limitation in studying the steric course of benzylpenicillinacylase (BPA)-catalyzed hydrolyses of *N*-(phenylacetyl)amino derivatives is the low solubility in aqueous solution. By using the more soluble *N*-(*p*-aminophenylacetyl) derivatives, the hydrolysis of some chiral primary amines (with known absolute configuration) could be examined and priority relations between the substituents at the asymmetric carbon atoms established. Independent use of priority sequences, established by the present method, and of chemical correlation, allowed absolute configuration *S* to be assigned to (+)-1-phenyl-2-butylamine.

In the previous work,[1] an approach to the use of benzylpenicillinacylase (BPA) for correlating absolute configurations was described. For this purpose the enzymatic deacylation of the *N*-phenylacetyl derivatives of a variety of amino compounds with known absolute configurations was reported. Hydrolysis results were analyzed by using the structure of Figure 1 (R = $CH_2C_6H_5$), which represents the configuration at the chiral center of the more rapidly hydrolyzed enantiomer. It was thus possible to assign positions A and B to each pair of substituents and to define the priority sequences based on the relation A > B. By following this method some priority relations useful for stereochemical correlations could be established.

Among the substrates examined to date, only the *N*-phenylacetyl derivatives of the amino acids did not show solubility problems in the aqueous reaction medium adopted for the enzymatic hydrolyses. For several of the other *N*-(phenylacetyl)amino derivatives the addition of methanol as co-solvent was necessary to circumvent this difficulty. By using the more soluble *N*-(*p*-aminophenylacetyl) derivatives, we present configurational correlations of certain chiral amines based on the relative rates of enzymatic hydrolysis of the enantiomers. Independent use of this method and of chemical correlation allowed absolute configuration *S* to be assigned to (+)-1-phenyl-2-butylamine.

Results and Discussion

In an attempt to define the *N*-acyl function useful for replacing the *N*-phenylacetyl group, we examined the influence of several *N*-acyl groups on the susceptibility of glycine and alanine derivatives to the hydrolytic action of BPA. The hydrolysis conditions and the results are reported in Table I. Acyl groups containing a free carboxyl group as polar substituent were first examined. The corresponding substrates (compounds **1–5**, Table I) resulted, practically unaffected by the enzyme. Even by using a high enzyme/substrate ratio, only in the case of compound **5** could a moderate hydrolysis be detected.

The use of *N*-acyl substituent containing a free primary amino group (see compound **6**, Table I) was successful. The hydrolysis rate found for the *N*-(*p*-aminophenylacetyl)alanine (**6**) was, in fact, of the same order as that found for the *N*-(phenylacetyl)alanine (**7**), one of the best substrates of BPA. In order to determine if the high susceptibility of the *p*-aminophenylacetyl group is retained even in the case of the derivatives of primary amines, the hydrolysis of *N*-(*p*-aminophenylacetyl)-2-aminobutane (**8**) was examined and compared with that of the *N*-(phenylacetyl)-2-aminobutane (**16**). The results reported in Table II show that on passing from **16** to **8** the stereoselectivity is preserved and the hydrolysis rate enhanced.

On the basis of the above results, we examined the enzymatic hydrolysis of the derivatives of the primary amines, having known absolute configuration, reported in Table III. The *N*-(*p*-aminophenylacetyl) derivatives were prepared with dicyclohexylcarbodiimide starting from *p*-(benzyloxycarbonylamino)phenylacetic acid and the amines. Palladium-catalyzed hydrogenolysis gave the desired compounds. The course of the enzymatic hydrolysis was followed by spectrophotometric determination of the *p*-aminophenylacetic acid produced. The hydrolyses were then interrupted and unhydrolyzed *N*-(*p*-aminophenylacetyl) derivatives were isolated. By comparing their optical rotations and those of corresponding *R* isomers, the stereochemical preference of the enzyme could be established. In the case of substrates **12** and **13** optical rotations of the amines released by the enzyme have been also utilized, because of the very low optical rotations of recovered *N*-(*p*-aminophenylacetyl) derivatives (see footnotes *d* and *i* of Table II).

Hydrolysis data were analyzed by referring to the structure of Figure 1 (R = $CH_2C_6H_4$-*p*-NH_2). A and B positions found for the substituents of each substrate are reported in Table III. From the hydrolysis data of compounds **8** and **10** the priority relations $CH_2CH_3 > CH_3$ and $CH_3 > C_6H_5$ can be deduced by using internal comparisons.[1,2] The relation $CH_2C_6H_5 > CH_2CH_3$ can be deduced from the data of optical purity relative to compounds **8** and **9** (Table II) by using external comparison.[1,2] As a result of these relations, sequence I follows:

$$CH_2C_6H_5 > CH_2CH_3 > CH_3 > C_6H_5$$

The three priority relations between noncontiguous terms of the sequence I (i.e., $CH_2C_6H_5 > CH_3$, $CH_2CH_3 > C_6H_5$, $CH_2C_6H_5 > C_6H_5$) can be verified by examining, by internal comparisons, the hydrolysis for compounds **9**, **11**, and **12**, respectively.

By examining hydrolytic results of substrate **14** the priority relation methyl > 2-naphthyl can be deduced. In the case of substrate **13**, optical rotations of the recovered *N*-(*p*-aminophenylacetyl) derivative and of the released amine show that BPA preferentially hydrolyzes the *S* enantiomer. The stereoselectivity found in this case seems, however, too low to be used as the basis of a configurational correlation.

Some of the relations found, such as methyl > phenyl, ethyl > phenyl, and benzyl > phenyl, are anomalous in terms of the usual concepts of sizes of the groups concerned[3] and these results show, in accordance with the observation reported in the previous paper,[1] that the relative arrangement of the

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Table I. Influence of Various *N*-Acyl Groups on the Susceptibility of Glycine and Alanine Derivatives of the Hydrolytic Action of BPA[a]

registry no.		RCONHCH(R′)COOH R	R′	mg	buffer, mL	enzyme, mg/mmol of substrate	incubn time, h	hydrolysis, %
5694-33-7	1	$(CH_2)_2COOH$	H	20	10	7.40	25	0
54930-24-4	2[b]	CH=CHCOOH (*Z*)	H	20	10	7.24	63	0
39829-03-3	(±)-3	CH=CHCOOH (*Z*)	CH_3	20	10	7.85	24	0
541-89-9	(±)-4	CH=CHCOOH (*E*)	CH_3	20	10	7.85	24	0
69622-04-4	(±)-5	$CH_2C_6H_4$-*p*-CH_2COOH	CH_3	20	10	11.00	24	7
69622-05-5	(±)-6	$CH_2C_6H_4$-*p*-NH_2	CH_3	20	10	0.93	0.5	44
17966-65-3	(±)-7	$CH_2C_6H_5$	CH_3	20	10	0.86	0.5	46

[a] Hydrolysis experiments were carried out in 0.1 M phosphate buffer, pH 7.0, and at a temperature of 37 °C. BPA = benzylpenicillinacylase. [b] See ref 9.

Table II. Hydrolytic Data Relative to *N*-Acylamino Compounds[a]

substrate no.	mg	buffer, mL	enzyme, mg/mmol of substrate	incubn time, h	hydrolysis, %	$[\alpha]_\lambda$, deg,[b] of substrates recovered	*R* isomers	registry no.	optical purity of recovered substrates, %[c]
(±)-8	640	380	1.16	8	51	−10 (*c* 5.0)	−21 (*c* 5.0)	69622-06-6	48
(±)-9	400	470	0.72	30	50	+4.2 (*c* 5.0)	+4.2 (*c* 5.0)	69622-07-7	100
(±)-10	500	600	2.10	30	50	−15.2 (*c* 5.0)	+82 (*c* 4.0)	52971-36-5	19
(±)-11	490	300	3.00	22	50	−70 (*c* 5.0)	+120 (*c* 4.0)	69622-08-8	58
(±)-12[d]	261	240[f]	10.50[e]	96	8	−0.9 (*c* 3.0)[g]	+33 (*c* 2.0)[g]	69622-09-9	3
(±)-13[i]	300	360[f]	4.40	76	25	Δε +0.18 (280 nm)[h]	Δε +4.4 (280 nm)	69622-10-2	4
(±)-14	330	400[f]	4.40	50	20	−29 (*c* 4.0)	+113 (*c* 4.0)	69622-11-3	26
(±)-15	600	360	1.60	24	40	+2.4 (*c* 5.0)			
(±)-16[j]	200	45	1.94	24	53	−9.2 (*c* 3.0)	−17 (*c* 3.0)	56572-17-9	

[a] Hydrolysis experiments were carried out in phosphate buffer, pH 6 at 37 °C unless otherwise indicated. [b] All values were determined in methanol at the sodium D line and at 20 °C unless otherwise specified. [c] $100[\alpha]_\lambda$ (obsd)/$[\alpha]_\lambda$ (max). [d] In this case the amine released by the enzyme was also isolated and optical rotation of the corresponding hydrochloride was measured: $[\alpha]^{20}_D$ −48.0° (*c* 0.87, ethanol). Maximum value reported in literature for (*R*)-1,2-diphenylethylamine hydrochloride is $[\alpha]^{25}_D$ −125.5° (*c* 0.97, ethanol): T. Sasaki, K. Kanematsu, Y. Tsuzuki, and K. Tanaka, *J. Med. Chem.*, **9**, 847 (1966). [e] The hydrolysis was initiated by the addition of 5.25 mg of BPA; after a 48-h reaction period an additional 5.25 mg of BPA was added. [f] To increase the solubility of this substrate, hydrolysis experiments were carried out at pH 5.5. [g] λ 546 nm. [h] Because of the low value of the $[\alpha]_D$ of substrate recovered, CD_{max} in methanol are reported. [i] In this case the amine released by the enzyme was also isolated: $[\alpha]^{20}_{436}$ −2.3° (*c* 1.2, hexane). *R* isomer: $[\alpha]^{20}_{436}$ +130° (*c* 1.0, hexane). [j] Hydrolysis experiments on this substrate were reported previously. See ref 1. Registry no.: 56649-69-5.

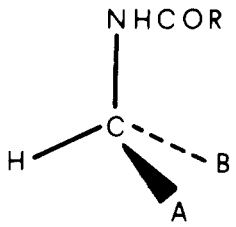
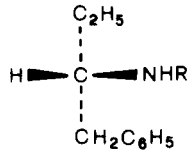


Figure 1. Configuration of the more rapidly hydrolyzed enantiomer; groups A and B are determined experimentally as given in Table III.

substituents in the A > B sequence is controlled, at least in part, by factors other than the size of groups.

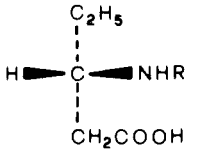
As an example of utilization of the defined priority sequences we report the configurational assignment made in the case of 1-phenyl-2-butylamine, whose absolute configuration has not yet been established. In order to make this assignment, we prepared and subjected to enzymatic hydrolysis *N*-(*p*-aminophenylacetyl)-1-phenyl-2-butylamine **[(±)-15]** (Table II). The optical rotation of the recovered *N*-(*p*-aminophenylacetyl) derivative was found to be $[\alpha]_D$ +2.4° (*c* 5, methanol). By referring to the structure of Figure 1 and assigning position A to the benzyl group and position B to the ethyl group (see sequence I) we can deduce *S*-(−) configuration for the more rapidly hydrolyzed enantiomer. A sample of (+)-1-phenyl-2-butylamine, $[\alpha]_D$ +9.14° (neat),[4] was then acylated to give *N*-(*p*-aminophenylacetyl)-1-phenyl-2-butylamine, $[\alpha]_D$ −1.2° (*c* 10, methanol). On the basis of this value of optical rotation we can assign configuration *S* to (+)-1-phenyl-2-butylamine.

In order to confirm the assignment of absolute configuration, the following chemical correlation has been established:



17, R = H

18, R = $COCH_3$



19, R = $COCH_3$

20, R = H

The (+)-1-phenyl-2-butylamine (**17**), $[\alpha]_D$ +9.14° (neat), has been acetylated to give (−)-*N*-acetyl-1-phenyl-2-butylamine (**18**), $[\alpha]_D$ −2.0° (*c* 2.0, methanol). Ozonization followed by oxidation of **18** with hydrogen peroxide afforded the (−)-*N*-acetyl-3-aminovaleric acid (**19**), $[\alpha]_D$ −3.6° (*c* 5.0, methanol). Since treatment of **19** with 2 N hydrochloric acid gave (*S*)-3-aminovaleric acid (**20**), $[\alpha]_D$ +6.0° (*c* 4.0, water),[5] configuration *S* was confirmed for (+)-1-phenyl-2-butylamine.

Table III. *N*-(*p*-Aminophenylacetyl)amino Derivatives with Known Absolute Configuration Subjected to Enzymatic Hydrolysis and Preferred Enantiomers

compd[a]	absolute configuration	preferred enantiomer A	preferred enantiomer B
N-*p*-APA-2-aminobutane (**8**)	*S*-(+)[b]	CH_2CH_3	CH_3
N-*p*-APA-1-benzylethylamine (**9**)	*S*-(−)[c]	$CH_2C_6H_5$	CH_3
N-*p*-APA-1-phenylethylamine (**10**)	*R*-(+)	CH_3	C_6H_5
N-*p*-APA-1-phenyl-*n*-propylamine (**11**)	*R*-(+)	CH_2CH_3	C_6H_5
N-*p*-APA-1,2-diphenylethylamine (**12**)	*R*-(+)	$CH_2C_6H_5$	C_6H_5
N-*p*-APA-1-(1-naphthyl)ethylamine (**13**)	*S*-(−)[d]	1-$C_{10}H_7$	CH_3
N-*p*-APA-1-(2-naphthyl)ethylamine (**14**)	*R*-(+)	CH_3	2-$C_{10}H_7$

[a] *p*-APA = *p*-aminophenylacetyl [b] Registry no.: 69622-12-4. [c] Registry no.: 69622-13-5. [d] Registry no.: 69622-14-6.

Table IV. Physical and Analytical Data for *N*-(*p*-Aminophenylacetyl)amino Derivatives[a]

compd, no.	registry no.	mp,[b] °C	yield,[c] %	$[\alpha]_D$, deg,[d] reaction product	$[\alpha]_D$, deg,[d] starting amine
(±)-**8**	69684-41-9	123–124	35		
(***R***)-**8**		117–119	33	−21 (*c* 5.0)	−7.8 (neat)
(±)-**9**	69684-42-0	135–136	33		
(***R***)-**9**		79–80	30	+4.2 (*c* 5.0)	−34 (neat)
(±)-**10**	69684-43-1	115–116	40		
(***R***)-**10**		142–143	25	+82 (*c* 5.0)	+40 (neat)
(±)-**11**	69684-44-2	oil[e]	35		
(***R***)-**11**		125–126	42	+120 (*c* 4.0)	+21 (neat)
(±)-**12**[f]		197–199[g]	35		
(***R***)-**12**[f]	69622-15-7	235–237[g]	37	+23.5 (*c* 2.4)	−126 (*c* 1.0, ethanol)[f,h]
(±)-**13**[f]		259–260[g]	15		
(***R***)-**13**		160–161	20	+20 (*c* 5.0)	+75 (neat)
(±)-**14**	69684-45-3	140–141	23		
(***R***)-**14**[f]	69622-16-8	206–208[g]	25	+113 (*c* 4.0)	+21 (*c* 2.0, ethanol)[i]
(±)-**15**[f]		200–201[g]	50		
(−)-**15**	69622-17-9	oil[j]	40	−1.2 (*c* 10)	+9.14 (neat)[k]
(±)-**6**[l]		205–206[m]	52		

[a] Satisfactory analytical data (±0.2% for C, H, N, Cl) were reported for all new compounds listed in this table, with exception of (±)-**13** (−0.47% for C). In the IR spectrum ($CHCl_3$) all compounds showed strong absorption at 3400, 2920, 1640, and 1500 cm^{-1}. [b] All compounds were crystallized from ethyl acetate–hexane unless otherwise specified. [c] Yield based on starting amine. [d] All values were determined in methanol at 20 °C unless otherwise specified. [e] Pure by TLC examination; the IR spectrum ($CHCl_3$) was identical with that of the (*R*)-**11**. [f] Hydrochloride salt. [g] Crystallized from ethanol–ether. [h] See reference cited in footnote *d* of Table II. [i] V. M. Potapov, V. M. Dem'yanovich, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **35**, 1538 (1965). [j] Pure by TLC examination; the IR spectrum ($CHCl_3$) was identical with that of (±)-**15**. [k] See ref 4. [l] Prepared from (±)-alanine methyl ester. [m] Crystallized from methanol.

Experimental Section

General. Melting points were determined in capillary tubes and are uncorrected. Preparative layer chromatography (PLC) was carried out with Merck HF_{254} silica gel on 0.5-mm thick plates. Optical rotations were obtained at 20 °C using a Perkin-Elmer 141 automatic polarimeter. IR spectra were recorded on a Perkin-Elmer 521 spectrophotometer. Colorimetric determinations were performed using a Beckman Model DU-2 spectrophotometer. Abbreviation of BPA for benzylpenicillinacylase was used throughout the work.

Hydrolysis Experiments. General Procedure. *N*-(*p*-Aminophenylacetyl)amino derivatives (**8–15**) were dissolved as hydrochlorides in water and pH was adjusted to the values reported in Table II with phosphate buffer (0.1 M, pH 7). A purified preparation of BPA[1] was then added, and the mixture was maintained at 37 °C in a thermostated water bath. The course of the reaction was monitored by determining, at suitable intervals, the *p*-aminophenylacetic acid produced. The following procedure was adopted. A 10-mL aliquot of the reaction mixture was concentrated to 5 mL and the pH was adjusted to 10 by the addition of 2 N aqueous sodium hydroxide. *N*-(*p*-Aminophenylacetyl)amino derivative and the amine released by the enzyme were then separated from *p*-aminophenylacetic acid by extraction with ethyl acetate. The *p*-aminophenylacetic acid present in the aqueous phase was determined using the colorimetric method reported by Bandelin and Kemp.[6]

After the incubation time reported in Table II for each substrate, the unaltered *N*-(*p*-aminophenylacetyl)amino derivative and the released amine were separated from *p*-aminophenylacetic acid as described above. The *N*-(*p*-aminophenylacetyl)amino derivative was separated from amine by PLC (eluent, ethyl acetate).

In the case of the *N*-acylamino derivatives **1–7**, hydrolysis experiments were carried out in 0.1 M phosphate buffer, pH 7.0, and at a temperature of 37 °C. The progress of the hydrolysis was followed by ninhydrin determination of released amino acid.

Preparation of *N*-(*p*-Aminophenylacetyl)amino Derivatives. General Procedure. Dicyclohexylcarbodiimide (12 mmol) was added to a stirred solution of *p*-(benzyloxycarbonylamino)phenylacetic acid[7] (12 mmol) and the amine (12 mmol) in dry chloroform (100 mL) at 0 °C. After 1 h at 0 °C and 4 h at room temperature the reaction mixture was filtered and the solution was washed with 1 N hydrochloric acid, aqueous sodium bicarbonate, and water. The organic layer was dried over Na_2SO_4 and evaporated to give a solid residue which was washed with ether in order to remove most of the soluble impurities. The crude [*p*-(benzyloxycarbonylamino)phenylacetyl]-amino derivative in dry methanol (90 mL) containing HCl (100 mmol) was hydrogenated in the presence of 10% Pd–C catalyst (470 mg) at atmospheric pressure for 4 h. The catalyst was removed and the solution was evaporated. Purification of the residue by PLC [eluent: chloroform–methanol–water (90:5:0.5)] gave the *N*-(*p*-aminophenylacetyl)amino derivative. The physical and analytical data are summarized in Table IV.

***N*-(3-Carboxypropionyl)glycine (1).** This was obtained by alkaline hydrolysis of ethyl (3-carboxypropionyl)glycinate:[8] mp 151–152 °C (methanol–ether); 65% yield.

Anal. Calcd for $C_6H_9NO_5$: C, 41.15; H, 5.18; N, 8.00. Found: C, 41.20; H, 5.25; N, 8.09.

***N*-(1-Carboxyethyl)maleamic Acid [(±)-3].** This compound was prepared according to the procedure reported by F. E. King and co-workers for *N*-(carboxymethyl)maleamic acid (**2**):[9] crystals from 2-butanol–hexane (50% yield); mp 144–145 °C.

Anal. Calcd for $C_7H_9NO_5$: C, 44.92; H, 4.85; N, 7.48. Found: C, 45.04; H, 5.02; N, 7.54.

***N*-(1-Carboxyethyl)fumaramic Acid [(±)-4].** Fumaric acid chloride monomethyl ester (2.0 g, 13.5 mmol) was added dropwise (1 h) to a stirred solution of (±)-alanine (1.1 g, 12.4 mmol) and $NaHCO_3$ (1.05 g, 12.4 mmol) in 7 mL of water at 0 °C. The solution was carefully maintained at pH 7.5 by adding 1 N NaOH. After washing with ether, the pH of the aqueous solution was adjusted to 10.0 with 2 N sodium hydroxide. After 4 h of stirring at room temperature the mixture was acidified with hydrochloric acid and extracted with ethyl acetate. The residue was crystallized from ethyl acetate (52% yield): mp 217–218 °C.

Anal. Calcd for $C_7H_9NO_5$: C, 44.92; H, 4.85; N, 7.48. Found: C, 44.85; H, 4.94; N, 7.50.

***N*-(*p*-Carboxymethylphenylacetyl)-(±)-alanine (5).** *p*-(Carbomethoxymethyl)phenylacetyl chloride (2.1 g, 9.2 mmol) was added to a stirred solution of (±)-alanine (0.7 g, 7.9 mmol) and pyridine (12 mL) in dimethylformamide (10 mL). The reaction mixture was stirred at room temperature overnight and evaporated. A solution of the residue in water was extracted with ethyl acetate and the organic layer was washed with 2 N hydrochloric acid and water. After removal of the solvent in vacuo, the residue was dissolved in methanol, sodium hydroxide (1.3 g in 2.0 mL of water) was added, and the mixture was stirred for 5 h at room temperature. The solvent was evaporated in vacuo and the residue was dissolved in water. The solution was acidified with hydrochloric acid and extracted with ethyl acetate. The residue was crystallized from water (30% yield): mp 215–216 °C.

Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.77; H, 5.80; N, 5.14.

(−)-*N*-Acetyl-1-phenyl-2-butylamine (18). (+)-1-Phenyl-2-butylamine (1.6 g, 10.7 mmol), $[\alpha]_D$ +9.14° (neat),[4] was dissolved in 6.4 mL of acetic anhydride. After standing for 2 days, the reaction mixture was treated with water and extracted with ether. The ethereal layer was washed with aqueous $NaHCO_3$ and water and dried (Na_2SO_4) to give, after evaporation, a crystalline residue, pure by TLC examination: 1.8 g (87% yield); $[\alpha]_D$ −2.0° (*c* 5.0, in methanol). Recrystallized from ether–hexane: mp 64–65 °C.

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.20; H, 8.98; N, 7.35.

(−)-*N*-Acetyl-3-aminovaleric Acid (19). A mixture of oxygen and ozone was passed into a solution of 2.0 g (10.4 mmol) of the compound **18**, $[\alpha]_D$ −2.0° (*c* 5.0, methanol), in 90 mL of acetic acid for 7 h at room temperature. The reaction mixture was left for 17 h at room temperature, then 3 mL of 30% hydrogen peroxide was added and the resulting mixture was allowed to stand overnight at room temperature. After evaporation to dryness, the oily residue was dissolved in aqueous sodium bicarbonate. The solution was washed with ether, acidified with hydrochloric acid, and extracted with ethyl acetate. After removal of the solvent under vacuum, the oily residue (1.1 g) was purified by column chromatography on silica gel (28 g). Elution with 9:1 ethyl acetate–benzene gave 0.4 g of impurities which were discarded; elution with 9:1 ethyl acetate–acetic acid gave the *N*-acetyl derivative **19** (0.6 g; 36.5% yield): $[\alpha]_D$ −3.4° (*c* 5.0, methanol). Recrystallized from ethyl acetate–hexane: mp 115–116 °C.

Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.91; H, 8.23; N, 8.89.

(+)-3-Aminovaleric Acid (20). (−)-*N*-Acetyl-3-aminovaleric acid (**19**), $[\alpha]_D$ −3.4° (*c* 5.0, methanol), was hydrolyzed by refluxing for 15 h in 2 N hydrochloric acid. Evaporation of the aqueous solution and treatment of the residue with Amberlite IR-4B gave a compound identical with an authentic specimen of 3-aminovaleric acid: $[\alpha]_D$ +6.0° (*c* 4.0, water).[5]

Registry No.—8 HCl, 69684-46-4; **9** HCl, 69684-47-5; **10** HCl, 69684-48-6; **11** HCl, 69684-49-7; **12** HCl, 69684-50-0; **13** HCl, 69684-51-1; **14** HCl, 69684-52-2; **15** HCl, 69684-53-3; **18**, 69622-20-4; **19**, 69622-21-5; **20**, 14389-77-6; benzylpenicillinacylase, 9014-06-6; *p*-(benzyloxycarbonylamino)phenylacetic acid 17859-70-0; (±)-2-butylamine, 33966-50-6; (±)-α-methylphenethylamine 300-62-9; (±)-α-methylbenzylamine, 618-36-0; (±)-α-ethylbenzylamine, 35600-74-9; (±)-α-phenylphenethylamine, 35373-59-2; (±)-α-methyl-1-naphthylmethylamine, 42882-31-5; (±)-α-methyl-2-naphthylmethylamine, 64234-21-5; (±)-α-ethylphenethylamine, 30543-88-5; ethyl 3-carboxypropionylglycinate, 69622-18-0; fumaric acid chloride, mono-methyl ester, 17081-97-9; (±)-alanine, 302-72-7; *p*-(carbomethoxymethyl)phenylacetylchloride, 69622-19-1; (+)-1-phenyl-2-butylamine, 30543-90-9; (*R*)-1,2-diphenylethylamine hydrochloride, 14149-01-0; (*R*)-1-(1-naphthyl)ethylamine, 3886-70-2.

References and Notes

(1) For part 1, see D. Rossi, A. Romeo, and G. Lucente, *J. Org. Chem.*, **43**, 2576 (1978).
(2) K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967).
(3) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971, p 87.
(4) Obtained by partial resolution of the hydrogen tartrate of racemic amine; maximum value reported for (−)-1-phenyl-2-butylamine is $[\alpha]^{20}_D$ −32° (neat): A. P. Terent'ev, G. V. Panova, G. N. Koval', and O. V. Toptygina, *Zh. Obshch. Khim.*, **40**, 1409 (1970).
(5) Maximum value reported in literature for (*S*)-3-aminovaleric acid is $[\alpha]_D$ +38.5° (*c* 2.9, water): G. Lucente, G. Piccinni, and A. Romeo, *Gazz. Chim. Ital.*, **96**, 1380 (1966).
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