Sterically Controlled Syntheses of Optically Active Organic Compounds. XIX. Asymmetric Syntheses of Amino Acids by the Strecker Reaction[1]

Kaoru HARADA, Tadashi OKAWARA, and Kazuo MATSUMOTO

Institute for Molecular and Cellular Evolution, and Department of Chemistry, 521 Anastasia Avenue, Coral Gables, Florida 33134, U.S.A.

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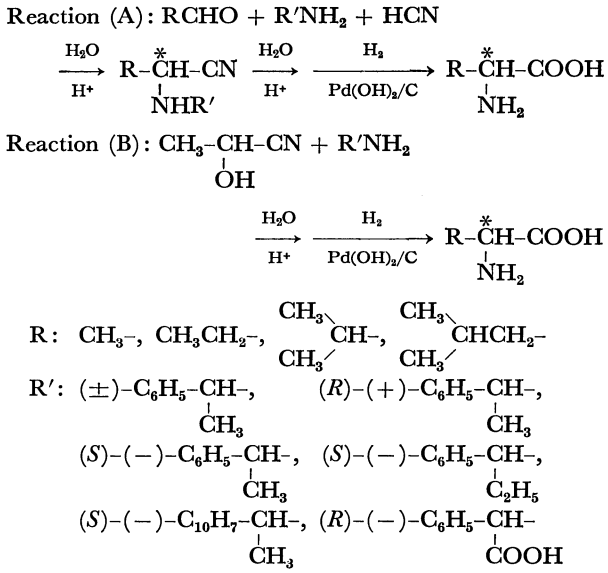
The Strecker type syntheses of optically active alanine, butyrine, valine, and leucine by the use of the corresponding aldehydes, hydrogen cyanide, and optically active α-alkylbenzylamines and α-(1-naphthyl)ethylamine were carried out (reaction A). The optical purities were in the range 22—51%. The modified Strecker type syntheses of alanine from acetaldehyde cyanohydrine and optically active amines were also carried out (reaction B). The optical purities of alanine were in the range 44—48%. In reaction B, optically active phenylglycine was also used as an amino source. The optical purities of the synthesized alanine were in the range 12—17%.

Synthesis of optically active alanine by the Strecker reaction using optically active α-methylbenzylamine, acetaldehyde, and hydrogen cyanide has been reported.[2] Optically active alanine was similarly synthesized from the same amine and racemic acetaldehyde cyanohydrine.[3] In these syntheses, the isolated alanine had rather high optical purities (80—95%), but the final products were isolated from the solution by crystallization. Thus, fractionation of optical isomers of alanine would be expected to take place during the crystallization process. Recently, the addition reaction of hydrogen cyanide to the Schiff bases of several aldehydes with optically active α-methylbenzylamines was studied.[4] It was reported that the isolated amino acids were almost optically pure. Although they claimed that there was no fractionation of the synthesized optical isomers during the isolation and purification processes, it was shown that fractionation could take place in three steps.[5] The real optical purities of amino acids prepared by the addition reactions of hydrogen cyanide were found to be much lower. Similar addition reactions of benzoyl cyanide to Schiff bases composed of various aldehydes and optically active α-alkylbenzylamine were studied.[6]

In the study of syntheses of optically active amino acids by the Strecker reaction, 1) the effect of the optically active moiety, 2) the effect of the aldehyde, and 3) the optical purity of the synthesized amino acids were investigated. Two kinds of reaction were carried out. A) the Strecker reactions of aldehydes, hydrogen cyanide, and optically active amines, and B) the modified Strecker reactions of racemic aldehyde cyanohydrine with optically active amines. The optically active amines used were: *R*-(+)-α-methylbenzylamine, *S*-(−)-α-methylbenzylamine, *S*-(−)-α-ethylbenzylamine, *S*-(−)-α-(1-naphthyl)ethylamine, and *R*-(−)-phenylglycine. The aldehydes used in reaction A were: acetaldehyde, propionaldehyde, isobutyraldehyde, and isovaleraldehyde. Reaction A was carried out in absolute ethanol at room temperature, except when the reactants were mixed at −10°C. Reaction B was carried out under similar conditions, except in reactions in which (*R*)-(−)-phenylglycine was used in aqueous alkaline conditions.



The resulting *N*-alkylaminonitriles synthesized in reactions A and B were hydrolyzed with 6 M hydrochloric acid. The resulting *N*-alkyl amino acids were then hydrogenolyzed with palladium hydroxide on charcoal to remove the *N*-alkyl residue. Free amino acids were isolated by the use of a Dowex 50 column. The free amino acids obtained were then converted into DNP-derivatives with 2,4-dinitrofluorobenzene, and the DNPylated amino acids were purified by means of celite column chromatography to avoid any fractionation of optical isomers. The optical purities of the resulting amino acids were measured using the DNP-amino acids.

The specific rotations, optical purities, and over-all yields of alanine, α-aminobutyric acid, valine, and leucine, by using optically active α-methylbenzylamine, α-ethylbenzylamine, and α-(1-naphthyl)ethylamine are given in Table 1. The over-all yields were in the range 19—47%. The optical purities of amino acids were in the range 22—51%. It seems that the optical purity of amino acids decreased as the size of the

1) Contribution No. 228 of the Institute for Molecular and Cellular Evolution.

2) K. Harada, *Nature*, **200**, 1201 (1963).
3) K. Harada and S. W. Fox, *Naturwissenschaften*, **51**, 106 (1964).
4) M. S. Patel and M. Worsley, *Can. J. Chem.*, **48**, 1881 (1970).
5) K. Harada and T. Okawara, *J. Org. Chem.*, **38**, 707 (1973).
6) K. Harada and T. Okawara, This Bulletin, **46**, 191 (1973).

TABLE 1. SYNTHESES OF OPTICALLY ACTIVE AMINO ACIDS BY THE STRECKER REACTION (REACTION A)

Aldehyde / Amine[a]	CH_3CHO Overall yld. (%)[b]	Config.	DNP-Ala[c] $[\alpha]_D^{25}$ (*c*, 1.6—2.4)	Optical purity (%)[d]	CH_3CH_2CHO Overall yld. (%)[b]	Config.	DNP-Buty[c] $[\alpha]_D^{25}$ (*c*, 1.6—2.0)	Optical purity (%)[d]
(R)-(+)-Me	42	(R)	−72.3	50	30	(R)	−50.5	51
(S)-(−)-Me	44	(S)	+68.2	47	32	(S)	+48.4	49
(S)-(−)-Et	47	(S)	+67.5	47	29	(S)	+50.5	51
(S)-(−)-Naph	45	(S)	+58.5	41	27	(S)	+35.6	36

Aldehyde / Amine[a]	$(CH_3)_2CHCHO$ Overall yld. (%)[b]	Config.	DNP-Val[c] $[\alpha]_D^{25}$ (*c*, 0.8—2.1)	Optical purity (%)[d]	$(CH_3)_2CHCH_2CHO$ Overall yld. (%)[b]	Config.	DNP-Leu[c] $[\alpha]_D^{25}$ (*c*, 1.7—5.6)	Optical purity (%)[d]
(R)-(+)-Me	17	(R)	−47.4	44	30	(R)	−12.8	22
(S)-(−)-Me	19	(S)	+49.1	45	32	(S)	+14.3	24
(S)-(−)-Et	26	(S)	+40.5	37	28	(S)	+23.4	39
(S)-(−)-Naph	24	(S)	+33.1	31	31	(S)	+14.7	25

a) (R)-(+)-Me, (R)-(+)-α-methylbenzylamine; (S)-(−)-Me, (S)-(−)-α-methylbenzylamine; (S)-(−)-Et, (S)-(−)-α-ethylbenzylamine; (S)-(−)-Naph, (S)-(−)-α-(1-naphthyl)ethylamine.
b) The yields are calculated from aldehydes.
c) Specific rotations of DNP-amino acids were measured in 1N NaOH.
d) Defined as $[\alpha]_D$ obsd/$[\alpha]_D$ of the compound × 100. DNP-(S)-(+)-Alanine, $[\alpha]_D^{25}$ +143.9° (1M NaOH); DNP-(S)-(+)-butyrine, $[\alpha]_D^{25}$ +98.8° (1M NaOH); DNP-(S)-(+)-valine, $[\alpha]_D^{25}$ +109.1° (1M NaOH); DNP-(S)-(+)-leucine, $[\alpha]_D^{25}$ +59.5° (1M NaOH).

alkyl group of the aldehydes increased. When (*R*)-(+)- or (*S*)-(−)-amine was used, (*R*)- or (*S*)-amino acid was synthesized. The effect of amines on the optical purities of the resulting amino acids was not clear; however, the effect of α-(1-naphthyl)ethylamine on the optical purities of the resulting amino acids seems lower than that of α-methyl- and α-ethylbenzylamine.

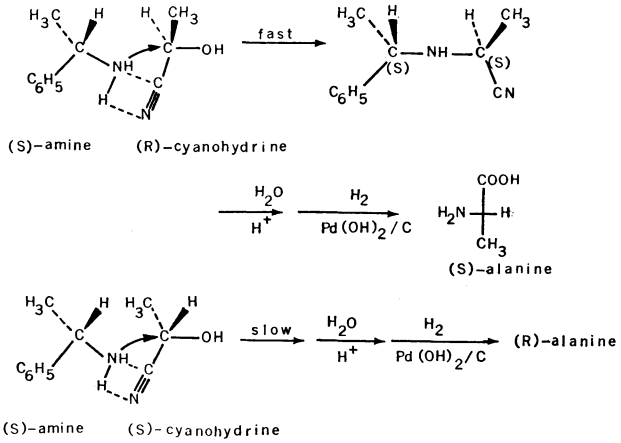
TABLE 2. SYNTHESIS OF OPTICALLY ACTIVE ALANINE FROM RACEMIC ACETALDEHYDE CYANOHYDRINE AND OPTICALLY ACTIVE AMINES (REACTION B)

$$CH_3\overset{(\pm)}{C}HCN + R\text{–}NH_2 \longrightarrow CH_3\overset{*}{C}HCN$$
$$\quad\quad OH \quad\quad\quad\quad\quad\quad NHR^*$$
$$\xrightarrow[H^+]{H_2O} CH_3\overset{*}{C}HCOOH \xrightarrow[Pd(OH)_2/C]{H_2} Ala$$
$$\quad\quad NHR^*$$

Amine[a]	Overall yield[b] (%)	DNP-Alanine Config.	$[\alpha]_D^{24}$ (1M NaOH)[c] (*c*, 1.7—1.8)	Optical purity[d] (%)
1. ±Me	54	±	—	—
2. (*R*)-(+)-Me	56	(R)	+62.7	44
3. (*S*)-(−)-Me	57	(S)	+64.1	44
4. (*S*)-(−)-Et	51	(S)	+69.2	48
5. (*S*)-(−)-Naph	38	(S)	+65.1	45

a) ±Me, racemic 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) The yields are calculated from acetaldehyde cyanohydrine.
c) Specific rotations of DNP-alanine were measured in 1M NaOH.
d) Defined as $[\alpha]_D$ obsd/$[\alpha]_D$ of the compound × 100. DNP-(*S*)-(+)-alanine, $[\alpha]_D^{25}$ +143.9° (1M NaOH).

The syntheses of optically active alanine from racemic acetaldehyde cyanohydrine with optically active amines (reaction B) are given in Table 2. When (*R*)-(+)-amine or (*S*)-(−)-amine was used, (*R*)- or (*S*)-alanine was synthesized as in reaction A. The optical purities were in the range 44—48%, and the over-all yields were in the range 38—57%. The results are very similar to those obtained in the synthesis of alanine in reaction A. Thus, it might be possible that the reaction mechanism of B is a stereoselective reaction between [(*S*)-amine and (*R*)-cyanohydrine] and [(*S*)-amine and (*S*)-cyanohydrine] as shown below:



When the amino group of the (*S*)-amine approaches the (*R*)- and (*S*)-cyanohydrines interacting with the nitrile group, the (*S*)-amine more easily attacks the

Table 3. Synthesis of optically active alanine from acetaldehyde cyanohydrine and optically active amines under varying ratios of reactants

(*S*)-(−)-Me[a] (0.01 mol)	Racemic lacto-nitrile (0.01 mol)	Yield[b] (%)	DNP-Alanine $[\alpha]_D^{25}$ (1M NaOH) (*c*, 0.4—0.5)	Optical purity[c] (%)
3	1	29	+61.80	43
2	1	26	+48.60	34
1	1	28	+61.54	43
1	2	30	+55.0	38
1	3	31	+45.89	32
1	4	35	+37.2	26
1	5	35	+31.6	22
1	10	34	+33.7	23

(*S*)-(−)-Et[a] (0.01 mol)	Racemic lacto-nitrile (0.01 mol)	Yield[b] (%)	DNP-Alanine $[\alpha]_D^{25}$ (1M NaOH) (*c*, 0.4—0.5)	Optical purity[c] (%)
2	1	28	+63.8	44
1	1	26	+64.5	42
1	2	28	+60.2	42
1	3	29	+44.3	31
1	4	28	+41.7	29

a) (*S*)-(−)-Me, (*S*)-(−)-α-methylbenzylamine; (*S*)-(−)-Et, (*S*)-(−)-α-ethylbenzylamine.
b) The yields are calculated from the least reactant (0.01 mol).
c) Defined as $[\alpha]_D$ obsd/$[\alpha]_D$ of the compound × 100. DNP-(*S*)-(+)-alanine, $[\alpha]_D^{25}$ +143.9° (1M NaOH).

Table 4. Synthesis of optically active alanine from racemic acetaldehyde cyanohydrine using (*R*)-(−)-phenylglycine

(*R*)-(−)-Phe-Glycine (0.01 mol)	Racemic lacto-nitrile (0.01 mol)	Yield[a] (%)	DNP-(*S*)-Alanine $[\alpha]_D^{25}$ (1M NaOH) (*c*, 0.3—0.5)	Optical purity[b] (%)
4	1	77	+17.8	12
3	1	73	+23.2	16
2	1	62	+20.0	14
1	1	56	+24.1	17
1	2	67	+23.8	17
1	3	82	+21.6	15
1	4	85	+20.0	14
1	5	75	+21.9	15

a) The yields are calculated from the least reactant (0.01 mol).
b) Optical purity defined as $[\alpha]_D$ obsd/$[\alpha]_D$ of the compound × 100. DNP-(*S*)-(+)-alanine, $[\alpha]_D^{25}$ +143.9° (1M NaOH).

α-carbon of (*R*)-cyanohydrine than (*S*)-cyanohydrine because of steric factors. The (*S*)-amine reacts with (*R*)-cyanohydrine to form *N*-(*S*)-α-methylbenzyl-(*S*)-aminopropionitrile which was hydrolyzed and hydrogenolyzed to form (*S*)-alanine. However, this mechanism is not likely, because reactions carried out at a higher ratio of cyanohydrine to amine did not yield higher optical purities of alanine, but rather lower values as shown in Tables 3 and 4. On the other hand, the dissociation of cyanohydrine to aldehyde and hydrogen cyanide should be considered. The yields and optical purities of alanine prepared from reactions A and B are almost the same; therefore, these reactions might proceed by the same reaction mechanism. The addition of hydrogen cyanide to Schiff bases composed of aldehydes and amines is a possible mechanism. Such a steric course has been described[7] but the mechanism is arbitrary. In order to understand the steric course of this reaction, *syn* and *anti* structures of the Schiff base must be determined under the reaction conditions. The results shown in Tables 1 and 2 indicate that the high optical purity of isolated alanine in the earlier reports[2,3] would be due to the fractionation during the final crystallization stage.

The Strecker type reaction was also carried out by the use of racemic lactonitrile with (*R*)-(−)-phenylglycine in aqueous conditions. The resulting *N*-substituted aminonitrile was hydrolyzed and hydrogenolyzed to convert the product into optically active alanine. The yields were rather high (56—85%); however, optical purities were low (12—17%). When (*R*)-(−)-phenylglycine was used, (*S*)-alanine was produced as in the case using (*S*)-(−)-α-methylbenzylamine.[8] The results are summarized in Table 4.

Experimental

All hydrogenolyses were carried out with a Parr 3910 Shaker type hydrogenation apparatus by using palladium hydroxide on charcoal or palladium on charcoal as a catalyst. All optical activity measurements were carried out on a JASCO ORD-CD-UV 5 spectropolarimeter.

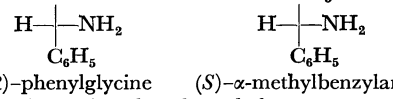
The specific rotations of optically active amines used were:
(*R*)-(+)-methylbenzylamine $[\alpha]_D^{25}$ +39.0°, benzene
(*S*)-(−)-methylbenzylamine $[\alpha]_D^{25}$ −38.5°, benzene
(*S*)-(−)-ethylbenzylamine $[\alpha]_D^{25}$ −20.0°, benzene
(*S*)-(−)-α-(1-naphthyl)ethylamine $[\alpha]_D^{25}$ −88.2°, benzene
(*R*)-(−)-phenylglycine $[\alpha]_D^{25}$ −168.0°, 5M HCl
Some of them are not completely optically pure (~95%); however, the optical purities of the resulting alanine are listed in the tables without corrections.

Syntheses of Amino Acids (Reaction A). To the solution of amine (0.012 mol) in absolute ethanol (20 ml) was added 1 ml of liqiud hydrogen cyanide (0.052 mol) at −10°C. Aldehyde (0.01 mol) was then added to the cold ethanolic solution. The sealed reaction mixture was shaken to homogenize the solution and was allowed to stand for 2 days at room temperature.

After the reaction was over, excess hydrogen cyanide and ethanol were evaporated under reduced pressure. The residue was refluxed with 20 ml of 6M hydrochloric acid for 12 hr. The hydrolyzate was extracted with ether to remove

7) In "Asymmetric Organic Reactions," by J. M. Morrison and H. S. Mosher, Prentice-Hall, Inc., Englewood Cliffs, New Jersey (1971), p. 328.

8) The steric structure of (*R*)-(−)-phenylglycine and (*S*)-(−)-α-methylbenzylamine could be expressed as shown below:



(*R*)-phenylglycine (*S*)-α-methylbenzylamine

If we regard the carboxyl and methyl groups as equivalent, the steric structures of (*R*)-(−)-phenylglycine and (*S*)-(−)-α-methylbenzylamine are the same.

Table 5. Elemental analyses of amino acids and *N*-alkyl amino acids

R: $\begin{matrix}CH_3\\ \vert\\ C_6H_5-CH-\end{matrix}$	Mp °C	Formula	Calcd (%)			Found (%)		
			C	H	N	C	H	N
N-*R*-Ala	275—276 (sublime)	$C_{11}H_{15}NO_2$	68.37	7.82	7.25	68.31	7.77	7.31
N-*R*-Buty	247—250 (sublime)	$C_{12}H_{17}NO_2$	69.54	8.27	6.96	69.61	8.23	6.88
N-*R*-Val	265—270 (sublime)	$C_{13}H_{19}NO_2$	70.56	8.65	6.33	70.18	8.85	6.34
N-*R*-Leu	256—258 (sublime)	$C_{14}H_{21}NO_2$	71.46	8.99	5.95	71.72	9.25	5.96
Ala	—	$C_3H_7NO_2$	40.44	7.92	15.72	40.20	7.86	15.49
Buty	—	$C_4H_9NO_2$	46.59	8.80	13.58	46.27	8.72	13.39
Val	—	$C_5H_{11}NO_2$	51.26	9.46	11.96	50.93	9.49	11.83
Leu	—	$C_6H_{13}NO_2$	54.94	9.99	10.68	54.91	9.87	10.64

colored material. The hydrochloric acid was evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of water and was applied to a Dowex 50 column (1.9 cm×23 cm, H^+ form) and eluted with 1.5 M aqueous ammonia. The fractions containing the amino acid were combined and the solution was evaporated under reduced pressure.

When optically active amines were used, the reaction products were treated in the same way. However, the resulting *N*-alkyl amino acids were not isolated to avoid fractionation of the diastereomeric mixture. The *N*-alkyl amino acids were dissolved in a mixture of ethanol and water (*ca.* 70 ml) and were hydrogenolyzed with 0.7 g of palladium hydroxide on charcoal for 12 hr. After hydrogenolysis was over, the catalyst was removed by filtration. The solution was evaporated under reduced pressure to give free α-amino acid. A part of the α-amino acid was converted into DNP-derivatives in the usual way. The resulting DNP-α-amino acids were purified by the use of a celite column treated with pH 7 citrate-phosphate buffer[9] to measure optical purities of resulting amino acids.

When racemic α-methylbenzylamine was used, the resulting racemic *N*-α-methylbenzylamino acids were isolated by means of a Dowex 50 column. Hydrogenolysis of these compounds with palladium hydroxide on charcoal resulted in the formation of racemic amino acids. The analytical results of these amino acids are summarized in Table 5. All of these *N*-substituted amino acids are sublimable at higher temperature.

Syntheses of Alanine (Reaction B). The freshly distilled racemic acetaldehyde cyanohydrine (0.71 g, 0.01 mol) and racemic amine were mixed with 20 ml of absolute ethanol under ice cooling. The reaction mixture was then kept at room temperature for 48 hr. After the reaction was over, ethanol was evaporated under reduced pressure. After evaporation of ethanol from the reaction mixture, the residue was dissolved in 20 ml of ethyl acetate. The solution was washed twice, with 20 ml of 1% aqueous sodium hydrogen carbonate, once with 20 ml of water and was dried over anhydrous sodium sulfate. The solution was evaporated under reduced pressure and distilled. When DL-α-methylbenzylamine was used, the DL-*N*-α-methylbenzylaminonitrile was isolated. Bp. 94—97°C/1.7 mmHg, yield, 1.2 g (66%). This was converted into its hydrochloride in ether treating with gaseous hydrogen chloride. The hydrochloride was recrystallized from ethanol. Mp. 141—142°C (decomp.).

Found: C, 62.43; H, 7.27; N, 13.40%. Calcd for $C_{11}H_{15}N_2Cl$: C, 62.70; H, 7.18; N, 13.30%.

The *N*-alkyl amino nitrile was hydrolyzed with 6 M hydrochloric acid. A part of the racemic *N*-α-methylbenzylalanine was isolated by means of a Dowex 50 column and recrystallized from ethanol and water for elemental analysis. Mp 270—273°C (sublime).

Found: C, 68.02; H, 7.71; N, 7.04%. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%.

The rest of the *N*-substituted alanine was then hydrogenolyzed by use of palladium hydroxide on charcoal and the alanine was isolated as in reaction A (Found: C, 40.47; H, 8.05; N, 15.77%).

Optically active alanine was prepared in a similar way to that described above. This was recrystallized from water and ethanol for elemental analysis (Found: C, 40.24; H, 8.00; N, 15.71%).

A part of the unfractionated alanine was converted into DNP-derivative, and was purified by the use of a celite column as in reaction A. The results are summarized in Table 2.

Synthesis of Alanine (Reaction B). Using (R)-(−)-Phenylglycine: (*R*)-(−)-Phenylglycine, 1.51 g (0.01 mol) was dissolved in 25 ml of water containing 0.01 mol of sodium hydroxide. To this solution, 0.71 g (0.01 mol) of racemic acetaldehyde cyanohydrine was added under cooling in an ice bath. The mixture was allowed to stand for 2 days at room temperature. To this, 30 ml of 6 M hydrochloric acid was added and refluxed for 6 hr. The hydrolyzate was evaporated to dryness under reduced pressure. The residue was dissolved in 50 ml of water containing 0.02 mol of sodium hydroxide. The solution was subjected to hydrogenolysis by using 2.0 g of 5% palladium on charcoal for 12 hr. After the hydrogenolysis was over, the catalyst was removed by filtration and the aqueous solution was acidified to a pH of about 2.0—1.5 and then evaporated to dryness. Synthesized alanine hydrochloride was extracted with absolute ethanol. The ethanolic solution was evaporated. The alanine hydrochloride was applied on a Dowex 50 column (H^+ form) and eluted with 1.5 M aqueous ammonia. Fractions containing alanine were combined and evaporated to obtain free alanine. A part of the alanine was DNPylated and the optical purity of alanine was measured as described earlier. The results are summarized in Table 4.

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9) J. C. Perrone, *Nature*, **167**, 513 (1951); A. Cout, *Biochem. J.*, **58**, 70 (1954).