Sterically Controlled Syntheses of Optically Active α-Amino Acids from α-Keto Acids by Reductive Amination[1]

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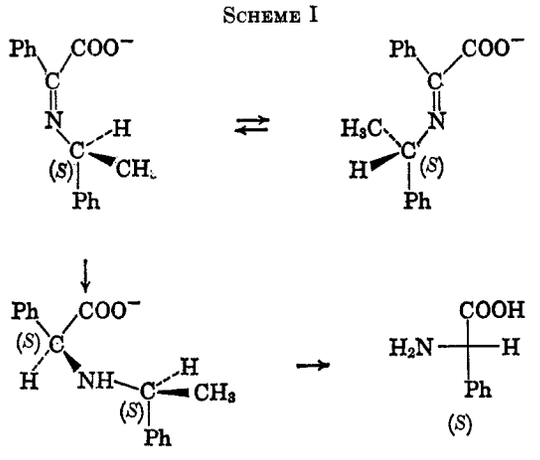
To clarify the steric courses of the asymmetric syntheses of α-amino acids from α-keto acids with optically active amines, three kinds of reactions were carried out: (A) hydrogenation of the Schiff bases of α-keto acids with (*S*)- and (*R*)-α-methylbenzylamine and with (*S*)- and (*R*)-α-ethylbenzylamine; (B) (1) hydrogenation of oximes of N-(*S*)- and -(*R*)-α-methylbenzylbenzoylformamide and of N-(*S*)- and -(*R*)-α-ethylbenzylbenzoylformamide; (2) hydrogenation of benzylamine Schiff bases of pyruvyl-(*S*)-alanine isobutyl ester and of pyruvyl-(*S*)- and -(*R*)-valine isobutyl ester; (C) hydrogenation of the Schiff bases of *l*-menthyl pyruvate with (*S*)- and (*R*)-α-methylbenzylamine and with (*S*)- and (*R*)-α-ethylbenzylamine. In each reaction, possible steric courses are discussed.

Several nonenzymatic asymmetric syntheses of α-amino acids from their corresponding α-keto acids have been reported.[2-6] Among these, relatively high optical purities of the resulting products were reported.[4-6] Hiskey and Northrop[4] demonstrated the synthesis of 12–80% optically active amino acids by catalytic hydrogenation and subsequent hydrogenolysis of the Schiff bases of α-keto acids with (*S*)-(−)- and (*R*)-(+)-α-methylbenzylamine. Harada[6] reported the syntheses of optically active amino acids in a way principally similar to those done by Hiskey but by the use of (*S*)- and (*R*)-α-phenylglycine in alkaline aqueous solution (optical purity 40–65%). These reactions are interesting because they are essentially a kind of asymmetric transamination reaction performed by catalytic hydrogenation and hydrogenolysis. Recently, Kanai and Mitsui[7] reported phenylglycine synthesis by the Hiskey reaction and proposed a steric course for the asymmetric synthesis, as illustrated in Scheme I.

SCHEME I



Hiskey and Northrop[8] reported alanylalanine formation from the Schiff base of benzylamine and pyruvyl-(*S*)-alanine by catalytic hydrogenation. They obtained (*R*)-alanyl-(*S*)-alanine and (*S*)-alanyl-(*S*)-alanine in the ratio 2:1 which was different from the results expected by the application of the Prelog rule.[9] Kanai and Mitsui[7] proposed the steric course of the reaction in which the two carbonyl groups of the pyruvyl-(*S*)-alanine might be in the cisoidal conformation.

In order to clarify the steric courses of the Hiskey-type syntheses[4,7,8] of optically active amino acids, three kinds of reactions were carried out: (A) hydrogenation of the Schiff bases of α-keto acids with (*S*)-(−)- and (*R*)-(+)-α-methylbenzylamine and with (*S*)-(−)- and (*R*)-(+)-α-ethylbenzylamine; (B) (1) hydrogenation of oximes of N-(*S*)-(−)- and -(*R*)-(+)-α-methylbenzylbenzoylformamide and of N-(*S*)-(−)- and -(*R*)-(+)-α-ethylbenzylbenzoylformamide and (2) hydrogenation of benzylamine Schiff bases of pyruvyl-(*S*)-(+)-alanine isobutyl ester and of pyruvyl-(*S*)-(+)- and -(*R*)-(−)-valine isobutyl ester; (C) hydrogenation of the Schiff bases of *l*-menthyl pyruvate with (*S*)-(−)- and (*R*)-(+)-α-methylbenzylamine and with (*S*)-(−)- and (*R*)-(+)-α-ethylbenzylamine.

Results and Discussion

In reaction A, many Hiskey-type reactions[4] were carried out in order to check the proposed steric course of Kanai and Mitsui.[7] Two kinds of optically active amines with different size alkyl groups, (*S*)- and (*R*)-α-methylbenzylamine and (*S*)- and (*R*)-α-ethylbenzylamine, were used as asymmetric centers of the syntheses. Optically active alanine (51–67%), α-amino-*n*-butyric acid (33–39%), phenylglycine (24–30%), phenylalanine (10–14%), and glutamic acid (6–12%) were obtained. Summarized data of reaction A are shown in Table I.

As is shown in Table I, the optical purities of the resulting amino acids in reaction A were dependent on the following: (a) as the size of the alkyl group of the α-keto acids became larger, the optical purity of the α-amino acid decreased in this order: Me > Et > Ph > $PhCH_2$ > CH_2CH_2COOH; (b) α-methylbenzyl-

(1) Sterically controlled synthesis of optically active organic compounds V. For part IV, see K. Harada, *J. Org. Chem.*, **32**, 1790 (1967). Contribution No. 076 of the Institute of Molecular Evolution, University of Miami.

(2) F. Knoop and C. Martius, *Z. Physiol. Chem.*, **258**, 238 (1939).

(3) J. B. Herbst and E. A. Swart, *J. Org. Chem.*, **11**, 366 (1946).

(4) R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.*, **83**, 4798 (1961).

(5) K. Matsumoto and K. Harada, *J. Org. Chem.*, **31**, 1956 (1956).

(6) K. Harada, *Nature*, **212**, 1571 (1966); part IV.[1]

(7) A. Kanai and S. Mitsui, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **89**, 183 (1966).

(8) R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.*, **87**, 1753 (1965).

(9) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953); V. Prelog, O. Ceder, and M. Wilhelm, *ibid.*, **38**, 303 (1955). The Prelog rule might not be applicable for the catalytic hydrogenation of the amides described in this work. The term "application of the Prelog rule" means that the conformation of the substrate is transoidal.

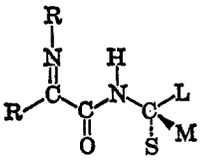


TABLE I

α-AMINO ACIDS PREPARED BY REACTION A

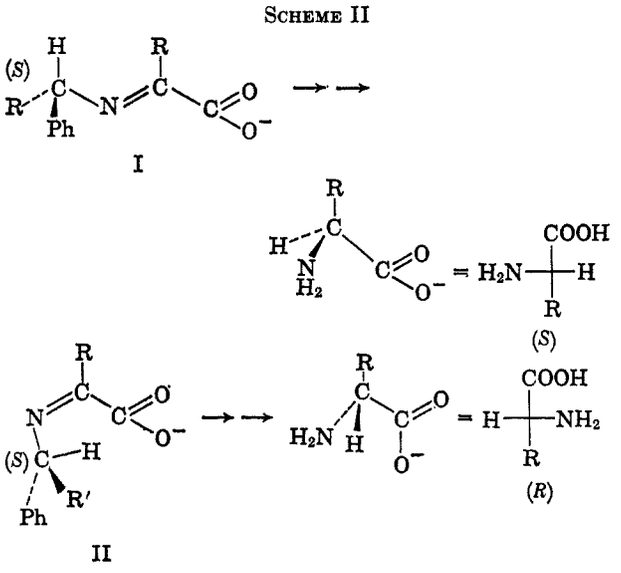
R in RCOCOOH	Confign of amine[a]	Yield, %	Confign of amino acid	Isolated amino acid, $[\alpha]^{25}D$, deg (c, 5 N HCl)[b]	Optical purity[d]	Dinitrophenyl-amino acid, $[\alpha]^{25}D$, deg (c, 1 N NaOH)[e]	Optical purity,[g]
CH_3	Me (−)	78	S (+)	+9.2 (3.55)	63	+96.9 (0.33)	67
	Et (−)	76	S (+)	+7.5 (3.46)	52	+72.8 (0.57)	52
	Me (+)	76	R (−)	−11.2 (4.10)	77	−93.3 (0.33)	65
	Et (+)	72	R (−)	−5.7 (2.72)	39	−72.7 (0.55)	51
C_2H_5	Me (−)	72	S (+)	+7.7 (3.80)	37	+28.5 (0.34)	39
	Et (−)	69	S (+)	+7.4 (3.13)	36	+32.4 (0.37)	33
	Me (+)	70	R (−)	−7.9 (3.25)	38	−36.6 (0.35)	37
	Et (+)	68	R (−)	−8.0 (3.81)	39	−35.6 (0.35)	36
C_6H_5	Me (−)	73	S (+)	+47.6 (2.51)	28	−36.0 (0.89)[f]	30
	Et (−)	70	S (+)	+42.2 (2.68)	25	−28.8 (0.34)[f]	24
	Me (+)	73	R (−)	−48.5 (2.31)	29	+36.6 (0.77)[f]	31
	Et (+)	69	R (−)	−40.5 (1.98)	24	+30.4 (1.25)[f]	26
$C_6H_5CH_2$	Me (−)	73	S (−)	−3.8 (1.78)[c]	12	+14.3 (0.48)[f]	14
	Et (−)	70	S (−)	−1.4 (2.10)[c]	5	+10.0 (0.37)[f]	10
	Me (+)	71	R (+)	+4.2 (1.42)[c]	13	−14.2 (0.38)[f]	14
	Et (+)	71	R (+)	+1.7 (2.30)[c]	5	−11.1 (0.54)[f]	11
CH_2CH_2COOH	Me (−)	74	S (+)	+4.2 (3.55)	13	−9.6 (0.68)[f]	12
	Et (−)	75	S (+)	+0.5 (5.31)	2	−5.2 (0.58)[f]	6

[a] Me (−), (*S*)-(−)-α-methylbenzylamine ($[\alpha]^{25}D$ −42.3°, benzene); Me (+), (*R*)-(+)-α-methylbenzylamine ($[\alpha]^{25}D$ +41.5°, benzene); Et (−), (*S*)-(−)-α-ethylbenzylamine ($[\alpha]^{25}D$ −21.0°, benzene); Et (+), (*R*)-(+)-α-ethylbenzylamine ($[\alpha]^{25}D$ +21.7°, benzene). [b] Optical rotations of first isolated amino acids were listed. [c] Optical rotations were measured in water. [d] Defined as ($[\alpha]D$ observed/$[\alpha]D$ literature) × 100. (*S*)-Ala, $[\alpha]^{25}D$ +14.6° (5 *N* HCl); (*S*)-α-NH_2-But, $[\alpha]^{25}D$ +20.6° (5 *N* HCl); (*S*)-Ph-Gly, $[\alpha]^{25}D$ +168° (5 *N* HCl); (*S*)-Phe, $[\alpha]^{25}D$ −34.5° (H_2O); (*S*)-Glu, $[\alpha]^{25}D$ +31.8° (5 *N* HCl): J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1961 (alanine, p 1819; α-aminobutyric acid, p 2401; phenylglycine, p 2697; phenylalanine, p 2156; glutamic acid, p 1929). [e] Dinitrophenylamino acids were isolated by column chromatography. Specific rotations were measured without further purification. [f] Optical rotations were measured in glacial acetic acid. [g] Defined as ($[\alpha]D$ observed/$[\alpha]D$ literature) × 100. DNP-(*S*)-Ala, $[\alpha]D$ +143.9° (1 *N* NaOH); DNP-(*S*)-α-NH_2-But, $[\alpha]D$ +98.8° (1 *N* NaOH); DNP-(*S*)-Phe, $[\alpha]D$ −103.3° (AcOH); DNP-(*S*)-Glu, $[\alpha]D$ −80.8° (AcOH): K. R. Rao and H. A. Sober, *J. Am. Chem. Soc.*, **76**, 1328 (1954); DNP-(*R*)-Ph-Gly, $[\alpha]^{25}D$ +119.2° (AcOH).

amine resulted in higher optical purity in each amino acid synthesis than that prepared with α-ethylbenzylamine. If the conformation proposed by Kanai and Mitsui[7] (Scheme I) is applicable in each synthesis of reaction A, then their proposed conformation does not agree with the results obtained in the present study. If their proposed conformation is correct, increase of the bulkiness of the alkyl group of the α-keto acids may not affect the optical purity of the resulting amino acids. If the proposed conformation is correct, α-ethylbenzylamine should result in a higher optical purity than that obtained by α-methylbenzylamine, which is contrary to the observation in this study.

The observed results of the present study suggest the possible conformations of reaction A to be structures I and II in Scheme II. Structure I might be the most predominant structure and structure II might be a minor structure. Structure II could be crowded because the bulky positively charged α-alkylbenzylamine could be located around the charged carboxylate ion. Structure I resulted in (*S*)-amino acid when (*S*)-amine was used. On the other hand, structure II resulted in (*R*)-amino acid when (*S*)-amine was used. When the alkyl group of α-keto acid is methyl (pyruvic acid), conformation of the reactant might be composed mainly of structure I, therefore resulting in highly optically active alanine. However, if the alkyl group is replaced

SCHEME II



with ethyl, phenyl, or benzyl, the optical purity decreases in that order. The contribution of structure II might increase owing to the steric hindrance between the alkyl group of α-keto acid and the hydrogen atom attached to the asymmetric carbon of the amine in structure I. However, according to the experimental

TABLE II

α-PHENYLGLYCINE PREPARED BY REACTION B1

Confign of amine[a]	Yield, %	Confign of amino acid	Isolated amino acid, $[\alpha]^{25}D$, deg (c, 5 N HCl)[b]	Optical purity,[c] %	Dinitrophenyl-phenylglycine, $[\alpha]^{25}D$, deg (c, AcOH)[d]	Optical purity,[e] %
Me (S)-(−)	56	(R)-(−)	−2.3 (2.62)	1.5	+6.1 (0.82)	5.5
Et (S)-(−)	52	(S)-(+)	+2.2 (2.61)	1.4	−9.7 (0.35)	8.8
Me (R)-(+)	53	(S)-(+)	+1.2 (2.87)	0.8	−5.4 (0.91)	4.9
Et (R)-(+)	48	(R)-(−)	−3.3 (2.67)	2.1	+11.1 (0.37)	10.0

[a] Me (−), (S)-(−)-α-methylbenzylamine ($[\alpha]^{25}D$ −42.3°, benzene); Me (+), (R)-(+)-α-methylbenzylamine ($[\alpha]^{25}D$ +41.5°, benzene); Et (−), (S)-(−)-α-ethylbenzylamine ($[\alpha]^{25}D$ −21.0°, benzene); Et (+), (R)-(+)-α-ethylbenzylamine ($[\alpha]^{25}D$ +21.7° benzene). [b] Optical rotations of first isolated amino acid were listed. [c] Defined as ($[\alpha]D$ observed/$[\alpha]D$ literature) × 100. (S)-Ph-Gly, $[\alpha]^{25}D$ +168° (5 N HCl): J. P. Greenstein and M. Winitz, footnote *d*, Table I, p 2697. [d] DNP-amino acids were isolated by column chromatography. Specific rotations were measured without further purification. [e] Defined as ($[\alpha]D$ observed/$[\alpha]D$ literature) × 100. DNP-(R)-Ph-Gly, $[\alpha]^{25}D$ +119.2° (AcOH): ref 5.

results, structure I seems to be a major conformation in each reaction.[10]

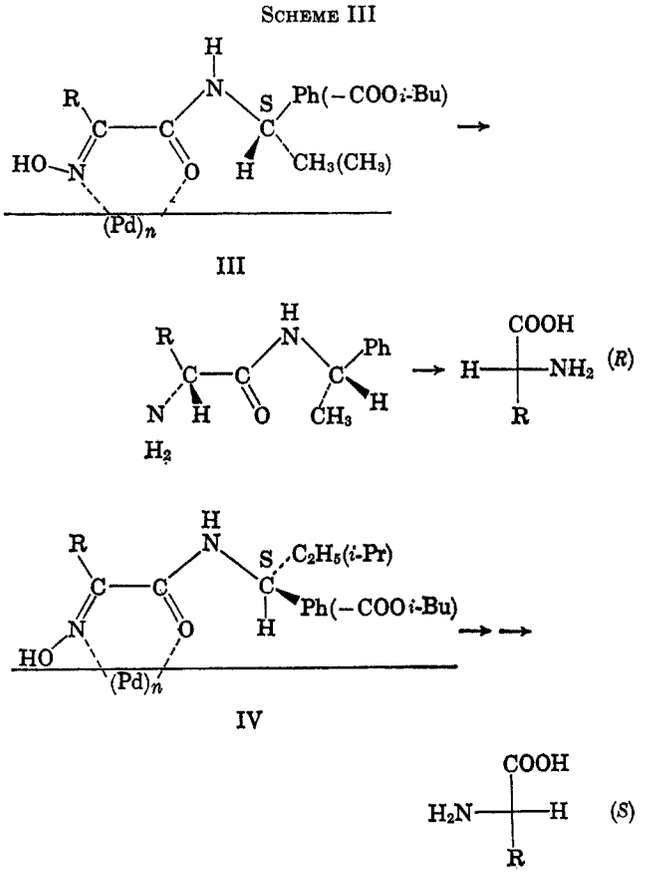
The decrease of optical purity by replacing α-methylbenzylamine with α-ethylbenzylamine could also be explained by the use of structure I. When a methyl group is replaced with an ethyl group, the relative ratio of bulkiness to the phenyl group decreases and the decrease of relative bulkiness reflects the decrease in optical purity of the product.

Hiskey and Northrop[8] discussed the mechanism of the alanylalanine synthesis from the Schiff base of benzylamine and pyruvyl-(S)-alanine, which was similar to the present study. However, they did not propose a definite steric course for the synthesis. Kanai and Mitsui[7] suggested that the C=N bond of the Schiff base and the C=O bond of the amide might be in the same direction (cisoidal conformation); however, no reasons have been given for the apparently unusual cisoidal conformation.

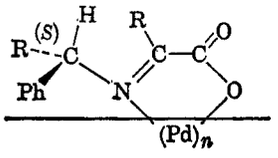
In reaction B1, optically active phenylglycine (5–10%) was obtained by hydrogenation of the oximes of N-(S)- and -(R)-α-methylbenzylbenzoylformamide and of N-(S)- and -(R)-α-ethylbenzylbenzoylformamide. When optically active (S)- or (R)-α-methylbenzylamines were used, the configurations of the resulting phenylglycines were (R) and (S), respectively, which were antipodes to those expected by application of the Prelog rule.[9] However, when (S)- and (R)-α-ethylbenzylamine were used, the resulting phenylglycines were (S) and (R) which agreed with the configurations expected by the application of the Prelog rule (Table II).

It seems reasonable to assume that both structures III and IV could take a cisoidal conformation as illustrated in Scheme III. The carbonyl group of the amide bond is partially charged, because the amide bond would be regarded as a resonance hybrid of the lactam [C(=O)NH] and dipolar [C(O⁻)=N⁺H] structures.[11] Therefore the carbonyl group and hydroxyimino group might be adsorbed on the catalyst surface to form a five-membered, rigid, ring-like structure.[12] Then the cyclic complex molecule could be

SCHEME III



(10) Structure I might form a five-membered cyclic structure with the catalyst as is shown in reaction B. Then the structure would be adsorbed

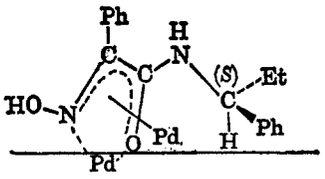


structure I

at the less bulky side of the molecule. The configurations of the resulting products with and without considering the cyclic intermediate complex are the same. When (S)-amine was used, (S)-amino acid would be the result. On the other hand, structure II might not form such a cyclic structure very easily because of the steric hindrance. The difference in the ease of formation of the cyclic complex between structures I and II might be an important factor explaining why structure I is a major conformation in the reaction. Formation of the cyclic intermediate complex of structure I seems to be possible sterically according to the "Dreiding stereomodel."

(11) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 281.

(12) Rigid, ring-like structure formation of the substrate on the palladium catalyst was discussed by Hartung: Y. Chang and W. H. Hartung, *J. Am. Chem. Soc.*, **75**, 89 (1953). The rigid, ring-like structure of the substrate on the catalyst surface might be regarded as a kind of organometallic compound as illustrated.



adsorbed on the less bulky side of the molecule. Hydrogen would attack the molecule from the front side of the paper and the *cis* addition of hydrogen would result in (*R*)-amino acid. However, structure IV resulted in (*S*)-amino acid. This might be explained as illustrated in Scheme III. The ethyl group is bulkier than the methyl group and the conformation of the optically active amine of IV might not exist as in structure III, and the least bulky hydrogen might be situated at the closest position to the catalyst because of the steric hindrance as is shown in Scheme III. Structure IV might also form a rigid, five-membered, ring-like structure with the catalyst, as might structure III. Therefore, structure IV will result in (*S*)-amino acid. The results in appearance agree with the results expected by employing the Prelog rule;[9] however, structure IV in the steric course of the reaction might be cisoidal as illustrated in Scheme III. To confirm the possible steric course of this reaction, benzylamine Schiff bases of pyruvyl-(*S*)-alanine isobutyl ester and pyruvyl-(*S*)- and -(*R*)-valine isobutyl ester were hydrogenated. When (*S*)-alanine isobutyl ester was used as an asymmetric center, the configuration of the resulting alanine was (*R*). When (*S*)- and (*R*)-valine isobutyl esters were used, (*S*)- and (*R*)-analine were obtained (Table III). These results are the same as obtained in the previous phenylglycine synthesis. The clear difference of the configuration of the product by the use of α-methyl- and α-ethylbenzylamine and also by the use of alanine isobutyl ester and valine isobutyl ester might be due to the strong interaction and steric hindrance between the molecule and the catalyst. Assumed conformations of structures III and IV in the form of "Dreiding stereomodels" seem to be reasonable to explain the configurations of the reaction products. In a similar way, alanylalanine synthesis[8] could be explained as illustrated below. The results of reaction B are summarized in Tables II and III (Scheme IV).

TABLE III

OPTICALLY ACTIVE α-ALANINE PREPARED BY REACTION B2

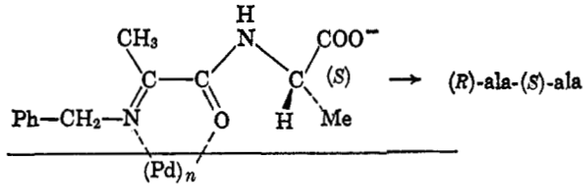
Substrate[a]	Yield,[b] %	Confign of alanine	Dinitrophenyl alanine, $[\alpha]^{25}D$, deg (*c*, 1 *N* NaOH)[c]	Optical purity,[d] %
Ala (*S*)-(+)	15	(*R*)-(−)	...	64[e]
Val (*S*)-(+)	11	(*S*)-(+)	+45.5 (0.45)	32
Val (*R*)-(−)	12	(*R*)-(−)	−45.4 (0.43)	32

[a] Ala (*S*)-(+), N-pyruvyl-(*S*)-(+)-alanine isobutyl ester; Val (*S*)-(+), N-pyruvyl-(*S*)-(+)-valine isobutyl ester; Val (*R*)-(−), N-pyruvyl-(*R*)-(−)-valine isobutyl ester. [b] Yield of dipeptide from pyruvic acid. [c] Dinitrophenylvaline was isolated by column chromatography. [d] Defined as ($[\alpha]D$ observed/$[\alpha]D$ literature) × 100. DNP-(*S*)-(+)-Ala, $[\alpha]D$ +143.9° (1 *N* NaOH): K. R. Rao and H. A. Sober, footnote *g*, Table I. [e] Ratio of (*R*)-(−)-alanyl-(*S*)-(+)-alanine and (*S*)-(+)-alanyl-(*S*)-(+)-alanine (82:18).

In reaction C, catalytic hydrogenation of the Schiff bases of *l*-menthyl pyruvate with (*S*)- and (*R*)-α-methylbenzylamine and with (*S*)- and (*R*)-α-ethylbenzylamine was studied to check the steric effect of the methyl and ethyl group of α-alkylbenzylamine. As was observed in the previous study,[13] the (*R*)-amine group and *l*-menthyl residue cooperated with each

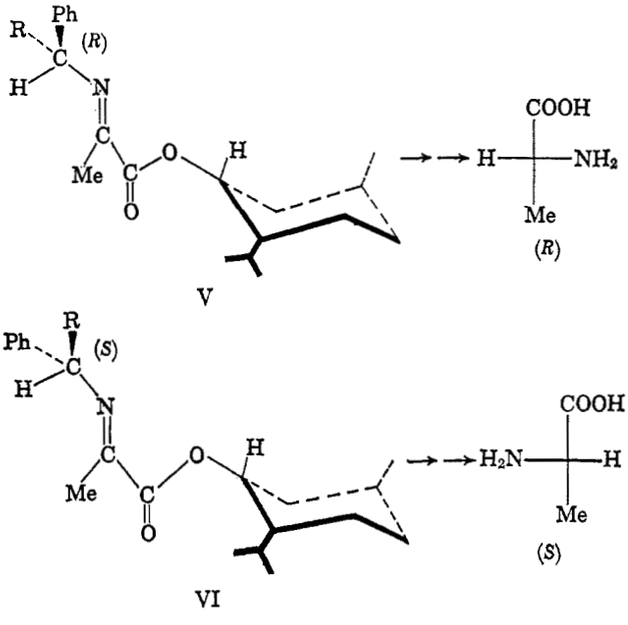
(13) Catalytic reduction of the Schiff base of (*S*)-(−) and of (*R*)-(+)-α-methylbenzylamine has already been studied.[5]

SCHEME IV



other to yield greater optical purity while (*S*)-amine and *l*-menthyl residues gave lower optical purity of the resulting amino acid. Steric effects due to the differences of methyl and ethyl groups were observed. In each, (*R*)- and (*S*)-α-methylbenzylamine resulted in a higher optical purity of alanine than that produced by the use of (*R*)- and (*S*)-α-ethylbenzylamine: (*R*)-α-methylbenzylamine (60%), (*R*)-α-ethylbenzylamine (36%), (*S*)-α-methylbenzylamine (19%), (*S*)-α-ethylbenzylamine (15%). Summarized results are shown in Table IV. The postulated steric course of reaction C is not a definite conclusion yet; however, structures V and VI in Scheme V are the most likely, because they are the least hindered sterically. In structure V, the (*R*)-amine and the menthyl groups cooperate with each other to yield a higher optical purity of the product; in structure VI, the steric effects of (*S*)-amine and the menthyl groups are reversed to give a lower optical purity. By the use of this possible conformation, it can be explained why the use of α-ethylbenzylamine resulted in lower optical purity than that obtained from α-methylbenzylamine.

SCHEME V



It has been observed that partially optically active amino acids are fractionated during the isolation and purification procedures.[5,6,14] To avoid the fractionation of optically active amino acids and to determine accurately the optical purity of the synthesized amino acids, a part of the product was directly treated with 1-fluoro-2,4-dinitrobenzene to yield dinitrophenylamino

(14) K. Harada and K. Matsumoto, *J. Org. Chem.*, **31**, 2985 (1966).

TABLE IV

Confign of amine[a]	Yield, %	Confign of amino acid	Isolated amino acid, $[\alpha]^{25}D$, deg (c, 5 N HCl)[b]	Optical purity[c]	Dinitrophenylalanine $[\alpha]^{25}D$, deg (c, 1 N NaOH)[d]	Optical purity[e]
Me (S)-(−)	57	(S)-(+)	+2.3 (3.19)	16	+26.4 (0.70)	19
Et (S)-(−)	56	(S)-(+)	+1.7 (2.40)	12	+20.2 (0.52)	15
Me (R)-(+)	61	(R)-(−)	−7.7 (3.41)	56	+82.3 (0.58)	60
Et (R)-(+)	55	(R)-(−)	−4.9 (2.67)	34	−50.0 (0.50)	36

[a] Me (−), (S)-(−)-α-methylbenzylamine ($[\alpha]^{25}D$ −42.3°, benzene); Me (+), (R)-(+)-α-methylbenzylamine ($[\alpha]^{25}D$ +41.5°, benzene); Et (−), (S)-(−)-α-ethylbenzylamine ($[\alpha]^{25}D$ −21.0°, benzene); Et (+), (R)-(+)-α-ethylbenzylamine ($[\alpha]^{25}D$ +21.7°, benzene). [b] Optical rotations of first isolated amino acid were listed. [c] Defined as ($[\alpha]D$ observed/$[\alpha]D$ literature) × 100. (S)-Ala, $[\alpha]^{25}D$ +14.6° (5 N HCl): J. P. Greenstein and M. Winitz, footnote *d*, Table I, p 1819. [d] Dinitrophenylamino acids were isolated by column chromatography. Specific rotations were measured without further purification. [e] Defined as ($[\alpha]D$ observed/$[\alpha]D$ literature) × 100. DNP-(S)-Ala, $[\alpha]D$ +143.9° (1 N NaOH): K. R. Rao and H. A. Sober, footnote *g*, Table I.

acids.[15] The resulting dinitrophenylamino acids were isolated chromatographically.[16] By the use of the dinitrophenyl method, accurate optical purities of the synthesized amino acids could be measured without fractionation during the isolation and purification procedures.

Racemization during the alkaline hydrolysis of the *l*-menthyl esters of the amino acids in reaction C has already been studied.[5] Racemization of phenylglycine in acid hydrolysis of phenylglycine amide in reaction B was also studied, because phenylglycine is one of the most easily racemizable amino acids. Under the conditions used in this study, it was found that 93% of optical purity was retained. By refluxing with hydrochloric acid under the same condition as above, (R)-(−)-phenylglycine retained 92% optical activity. Optical purities listed in Tables III and IV were all corrected by the use of the values of racemization of standard.

Experimental Section[17]

Reaction A. (S)-(+)-Alanine from Pyruvic Acid and (S)-(−)-α-Methylbenzylamine.—The (−)-α-methylbenzylamine[18,19] (2.42 g, 0.02 mole, $[\alpha]^{25}D$ −42.3°, benzene) in ethanol (30 ml) was added to pyruvic acid (0.88 g, 0.01 mole) in cold ethanol (40 ml). The mixture was allowed to stand for 30 min at room temperature. To the solution was added 10% palladium on charcoal (1.5 g), and then it was hydrogenated for 8 hr at room temperature. After 1 mole of hydrogen was absorbed, the catalyst was removed by filtration and washed with hot water. The combined solution was evaporated to 20 ml. To the concentrated solution was added 30% aqueous ethanol (50 ml) and palladium hydroxide on charcoal[4] (1.5 g). The hydrogenolysis was carried out at room temperature for 12 hr. The catalyst was removed by filtration and washed with hot water. The filtrate was concentrated to 5 ml *in vacuo*. Ethanol (30 ml) was added to the concentrate and the precipitating mixture was kept in a refrigerator for 1 day. (S)-(+)-Alanine was obtained: 0.70 g (78%), $[\alpha]^{25}D$ +9.2° (*c* 3.55, 5 N HCl).

Dinitrophenyl-(S)-(+)-alanine.—A part of the hydrogenolyzed solution (including about 0.15 g of alanine) was treated with 1-fluoro-2,4-dinitrobenzene (0.5 g) and sodium hydrogen carbonate (0.5 g) by the usual method.[15] Dinitrophenylalanine was separated by celite column chromatography by the same method described in a previous report:[5] $[\alpha]^{25}D$ +96.9° (*c* 0.33, 1 N NaOH), mp 171–173° dec.

(S)-(+)-Alanine from Pyruvic Acid and (S)-(−)-α-Ethylbenzylamine.—(S)-(+)-Alanine was prepared from (−)-α-ethylbenzylamine[20,21] (2.70 g, 0.02 mole, $[\alpha]^{25}D$ −21.0° benzene) in ethanol (30 ml) and pyruvic acid (0.88 g, 0.01 mole) in ethanol (40 ml) in the same way as above, 0.68 g (76%), $[\alpha]^{25}D$ +7.5° (*c* 3.46, 5 N HCl); dinitrophenyl-(S)-(+)-alanine had $[\alpha]^{25}D$ +72.8° (*c* 0.57, 1 N NaOH), mp 170–174° dec.

(S)-(+)-Phenylglycine from Benzoylformic Acid and (S)-(−)-α-Methylbenzylamine.—Benzoylformic acid (1.50 g, 0.01 mole) in absolute ethanol (40 ml) was added to (−)-α-methylbenzylamine (2.42 g, 0.02 mole) in absolute ethanol (30 ml). The mixture was allowed to stand for 4 days[22] at room temperature. To the mixture, 10% palladium on charcoal (1.5 g) was added, and then hydrogenation was carried out in the same way as above. After removing the catalyst by filtration, it was washed with hot water and then with 3 N hydrochloric acid (50 ml). To the combined filtrate and washing solutions, 2 N sodium hydroxide solution was added to bring the pH to about 4–5. The solution was concentrated to 70 ml. Ethanol (50 ml) was added to the concentrate. Hydrogenolysis using palladium hydroxide on charcoal (1.5 g) was carried out at room temperature. The catalyst was filtered. The filtrate was evaporated to dryness *in vacuo*. The dried residue was extracted with absolute ethanol (50 ml). The alcoholic solution was kept in a freezer overnight and the precipitated inorganic salt was removed by filtration. Pyridine was added to the filtrate to precipitate phenylglycine. After the suspension was kept in a cold room for 1 day, phenylglycine, 1.10 g (73%), was obtained, $[\alpha]^{25}D$ +47.6° (*c* 2.51, 5 N HCl); dinitrophenyl-(S)-(+)-phenylglycine had $[\alpha]^{25}D$ −36.0° (*c* 0.89, AcOH).

(S)-(+)-Glutamic Acid from α-Ketoglutaric Acid and (S)-(−)-α-Methylbenzylamine.—α-Ketoglutaric acid (1.46 g, 0.01 mole) in ethanol (40 ml) was added to (−)-α-methylbenzylamine (3.63 g, 0.03 mole) in ethanol (30 ml). The mixture was allowed to stand for 1 hr at room temperature. Hydrogenation and hydrogenolysis were carried out in the same way as described in earlier experiments. After hydrogenolysis, the catalyst was filtered and washed with water, The combined solution was evaporated to 20 ml. The concentrate was applied to a Dowex 50 × 2 column (hydrogen form, 100–200 mesh, 1.5 × 18 cm). Nonamino acid acidic components were eluted with water, then glutamic acid was eluted with 1 N ammonium hydroxide. Fractions of amino acid were evaporated to dryness. The residue was dissolved in a small amount of water and acetic acid was added to bring the pH to 3–4. Ethanol (30 ml) was added to the solution. The precipitating solution was allowed to stand in a cold room for 1 day. (S)-(+)-Glutamic acid (1.09 g, 74%) was obtained, $[\alpha]^{25}D$ +4.2° (*c* 3.55, 5 N HCl); dinitrophenyl-(S)-(+)-glutamic acid $[\alpha]^{25}D$ −9.6° (*c* 0.68, AcOH), mp 159–163° dec.

Reaction B1. N-(R)-(+)-α-Methylbenzylbenzoylformamide.—(+)-α-Methylbenzylamine (10 g, $[\alpha]^{25}D$ +41.5°, benzene) in benzene (30 ml) was added to a solution of benzoylformyl chloride (5.0 g) and benzene (70 ml) under violent stirring at a temperature below 10°. The evolving hydrogen chloride gas was removed under moderately reduced pressure. The mixture was stirred for 2 hr at room temperature. The precipitated crystals were removed by filtration. The benzene solution was washed with

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(22) Longer standing of the mixture at room temperature was found to be necessary to obtain a higher yield of amino acid. Short standing (30 min) did not give good results.

1 *N* hydrochloric acid and then water and dried with sodium sulfate. The benzene was evaporated and the amide was crystallized. After recrystallization from ethanol, 6.2 g (81.7%) pure (+)-amide was obtained: mp 112–113°, $[\alpha]^{25}D$ +107.6° (*c* 0.67, absolute EtOH).

Anal. Calcd for $C_{16}H_{15}NO_2$: N, 5.53. Found: N, 5.52.

N-(*S*)-(−)-α-Methylbenzylbenzoylformamide was obtained in 84.2% yield: mp 112–113°, $[\alpha]^{25}D$ −108.1° (*c* 0.72, absolute EtOH); lit.[23] mp 110–111°, $[\alpha]^{10}D$ −109.8° (absolute EtOH).

N-(*R*)-(+)-α-Ethylbenzylbenzoylformamide.—The compound was prepared in the same way as described above by the use of (+)-α-ethylbenzylamine:[20,21] ($[\alpha]^{25}D$ + 21.7°, benzene) in 50% yield: mp 88–90°, $[\alpha]^{25}D$ + 109.9° (*c* 0.95, absolute EtOH).

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.55; H, 6.48; N, 5.27.

N-(*S*)-(−)-α-Ethylbenzylbenzoylformamide was obtained in 54% yield: mp 88–89°, $[\alpha]^{25}D$ −108.7° (*c* 0.91, absolute EtOH).

(*R*)-(−)-Phenylglycine from Oxime of N-(*S*)-(−)-α-Methylbenzylbenzoylformamide.—The oxime of the (−)-amide was prepared as follows. A mixture of the (−)-amide (3.0 g), hydroxylamine hydrochloride (3.0 g), pyridine (25 ml), and absolute ethanol (25 ml) was refluxed for 3 hr in a water bath. Pyridine and ethanol were removed under reduced pressure. Water (20 ml) was added to the residue and the mixture was extracted with ethyl acetate. The ethyl acetate solution was dried and evaporated to dryness *in vacuo*. The residue (2.8 g) was used for the following experiment without purification. The (−)-amide oxime (2.68 g) was dissolved in ethanol (40 ml). The solution was hydrogenated with palladium hydroxide on charcoal (1.0 g) at room temperature. After the catalyst was removed by filtration, the ethanol was evaporated under reduced pressure. Hydrochloric acid (3 *N*, 60 ml) was added to the residue. The mixture was refluxed for 8 hr in an oil bath. After cooling, the mixture was extracted with ethyl acetate to remove any nonamino acid. The hydrochloric acid solution was treated in the same manner described earlier, 0.84 g (56%), $[\alpha]^{25}D$ −2.3° (*c* 2.62, 5 *N* HCl); dinitrophenyl-(*R*)-(−)-phenylglycine had $[\alpha]^{25}D$ +6.1° (*c* 0.82, AcOH).

Reaction B2. Amino Acid Isobutyl Ester *p*-Toluenesulfonates.—Isobutyl ester *p*-toluenesulfonates of optically active alanine and valine were prepared by the azeotropic method.[24] (*R*)-(−)-Alanine isobutyl ester *p*-toluenesulfonate was obtained in 84% yield: mp 118–120°, $[\alpha]^{25}D$ +1.2° (*c* 4.18, absolute EtOH).

Anal. Calcd for $C_{14}H_{23}NO_5S$: C, 52.98; H, 7.30. Found: C, 53.17; H, 7.37.

(*S*)-(+)-Alanine isobutyl ester *p*-toluenesulfonate was obtained in 78% yield: mp 118–120°, $[\alpha]^{25}D$ −1.1° (*c* 5.07, absolute EtOH).

Anal. Found: C, 52.97; H, 7.30.

(*R*)-(−)-Valine isobutyl ester *p*-toluenesulfonate was obtained in 81% yield: mp 144–146°, $[\alpha]^{25}D$ −100° (*c* 4.82, absolute EtOH).

Anal. Calcd for $C_{16}H_{27}NO_5S$: C, 55.63; H, 7.88. Found: C, 55.84; H, 7.95.

(*S*)-(+)-Valine isobutyl ester *p*-toluenesulfonate was obtained in 70% yield: mp 143–145°, $[\alpha]^{25}D$ +102° (*c* 5.36, absolute EtOH).

N-Pyruvyl-(*S*)-(+)-alanine Isobutyl Ester.—According to the method of Hiskey and Northrop,[8] N-pyruvyl-(*S*)-(+)-alanine isobutyl ester was prepared from (*S*)-(+)-alanine isobutyl ester *p*-toluenesulfonate (9.51 g, 0.03 mole), pyruvic acid (2.64 g, 0.03 mole), phosphorus oxychloride (2.75 ml, 0.03 mole), and pyridine (7.5 ml, 0.09 mole). The crude product was used for further experiment without purification.

(*R*)-(−)-Alanyl-(*S*)-(+)-alanine Isobutyl Ester.—To the above crude N-pyruvyl-(*S*-(+)-alanine isobutyl ester, benzylamine (3.21 g, 0.03 mole) and benzene (60 ml) were added. The mixture was refluxed for 20 min with a Dean–Stark separator. The benzene and excess benzylamine were removed *in vacuo*. The residue was diluted with methanol (30 ml) and methanolic hydrochloric acid was poured into the solution to bring the pH to 7–8. Hydrogenation and hydrogenolysis using 10% palladium on charcoal (2.5 g) were carried out for 2 days at room temperature. The catalyst was removed and the methanol was evaporated under reduced pressure. The residue was dissolved with ethyl acetate (30 ml) and then the ethyl acetate solution was washed with 1 *N* hydrochloric acid. To the aqueous solution, sodium hydrogen carbonate solution (5%) was added to bring the pH to 8. The solution was extracted with ethyl acetate. The solvent was evaporated under reduced pressure. The product was used for further experiments. The residue was diluted with methanol (80 ml).

(*R*)-(−)-Alanyl-(*S*)-(+)-alanine.—A part of the methanolic solution (20 ml) of the (*R*)-(−)-alanyl-(*S*)-(+)-alanine isobutyl ester was mixed with 2 *N* sodium hydroxide (2.5 ml) and allowed to stand for 24 hr at room temperature. Water (10 ml) was added and the methanol was evaporated under reduced pressure. The concentrate was applied to a Dowex 50 × 2 column (hydrogen form, 100–200 mesh, 1.5 × 1.8 cm). Nonamino acid acidic compounds were eluted with water; then (*R*)-(−)-alanyl-(*S*)-(+)-alanine was eluted with 1 *N* ammonium hydroxide. Fractions of alanylalanine were evaporated to dryness *in vacuo*, yielding 0.18 g (15% from pyruvic acid). The product was diluted with pure water (20 ml). The aqueous solution (1 ml) was diluted with pH 2.2 citrate buffer to 20 ml. The solution was used for the automatic amino acid analyzer (Phoenix K 5000) to determine the composition of two diastereomers of alanylalanine in the same way as previously reported.[8,25] The ratio of (*R*)-alanyl-(*S*)-alanine and (*S*)-alanyl-(*S*)-alanine was 82:18.

(*S*)-(+)-Alanyl-(*S*)-(+)-valine Isobutyl Ester.—Benzylamine (3.21 g, 0.03 mole) and benzene (60 ml) were added to the crude N-pyruvyl-(*S*)-(+)-valine isobutyl ester which was prepared from (*S*)-(+)-valine isobutyl ester *p*-toluenesulfonate (10.36 g, 0.03 mole) and pyruvic acid (2.64 g, 0.03 mole) by the same procedure described above. The mixture was refluxed for 20 min with a Dean–Stark separator. The reaction mixture was treated in the same way described for alanyl-(*S*)-(+)-alanine isobutyl ester. After hydrogenation and hydrogenolysis were carried out, the catalyst was filtered and the solvent was evaporated under reduced pressure. To the residue, 6 *N* hydrochloric acid (50 ml) was added and then the mixture was refluxed for 6 hr. The reaction mixture was evaporated to dryness under reduced pressure. The residue was treated with Dowex 50 × 2 column (hydrogen form, 100–200 mesh, 1.5 × 1.8 cm). A mixture of valine and alanine was obtained (0.65 g, 11% from pyruvic acid). After treatment with 1-fluoro-2,4-dinitrobenzene, the resulting dinitrophenylalanine and dinitrophenylvaline were separated by column chromatography.[5]

Dinitrophenyl-(*S*)-(+)-alanine had $[\alpha]^{25}D$ +45.5° (*c* 0.39, 1 *N* NaOH) (32% optically pure).

Dinitrophenyl-(*S*)-(+)-valine had $[\alpha]^{25}D$ +105.6° (*c* 0.45, 1 *N* NaOH) (97% optically pure); dinitrophenyl-(*S*)-(+)-valine had lit.[26] $[\alpha]D$ +109.2° (1 *N* NaOH).

Reaction C. (*S*)-(+)-Alanine from the Schiff Base of *l*-Menthyl Pyruvate with (*S*)-(−)-α-Ethylbenzylamine.—(*S*)-(+)-Alanine was prepared by hydrogenation of the Schiff base which was prepared from menthyl pyruvate (2.26 g, 0.01 mole) and (−)-α-ethylbenzylamine (1.35 g, 0.01 mole) in the same way as mentioned earlier,[5] yielding 0.45 g (56%), $[\alpha]^{25}D$ +1.7° (*c* 2.40, 5 *N* HCl); dinitrophenyl-(*S*)-(+)-alanine had $[\alpha]^{25}D$ +20.2° (*c* 0.52, 1 *N* NaOH), mp 171–174° dec.

Racemization of Phenylglycine.—A mixture of (*R*)-(−)-N-formyl phenylglycine (*S*)-(−)-α-methylbenzylamide[27] (2.0 g, 0.007 mole), and 3 *N* hydrochloric acid (60 ml) was refluxed for 8 hr in an oil bath. The reaction mixture was treated as described earlier, $[\alpha]^{25}D$ −155.4° (*c* 1.30, 5 *N* HCl); dinitrophenyl-(*R*)-(−)-phenylglycine had $[\alpha]^{25}D$ +110.4° (*c* 0.96, AcOH) (93% optically pure).

(*R*)-(−)-Phenylglycine ($[\alpha]^{25}D$ −168°, 5 *N* HCl) was heated in 3 *N* HCl under refluxing in an oil bath in the same condition as above, $[\alpha]^{25}D$ −152.3° (*c* 2.00, 5 *N* HCl); dinitrophenyl-(*R*)-(−)-phenylglycine had $[\alpha]^{25}D$ +110.0° (*c* 0.80, AcOH) (92% optically pure).

Registry No.—(*S*)-(+)-alanine, 10333-82-1; DNP-(*S*)-(+)-alanine, 10333-81-0; (*R*)-(−)-alanine, 10353-30-7; DNP-(*R*)-(−)-alanine, 10580-45-7; (*S*)-(+)-2-aminobutyric acid, 10385-46-3; DNP-(*S*)-(+)-2-

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(27) (*R*)-(−)-N-Formylphenylglycine (*S*)-(−)-α-methylbenzylamide was prepared from (*R*)-(−)-N-formylphenylglycine ($[\alpha]^{25}D$ −256°, EtOH) and (*S*)-(−)-α-methylbenzylamine by the use of dicyclohexylcarbodiimide in dioxane, mp 181–183°. *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: N, 9.92. Found: N, 10.27.

aminobutyric acid, 10549-02-7; (*R*)-(−)-2-aminobutyric acid, 10333-83-2; DNP-(*R*)-(−)-2-aminobutyric acid, 10549-04-9; (*S*)-(+)-α-phenylglycine, 2935-35-5; DNP-(*S*)-(+)-α-phenylglycine, 10549-06-1; (*R*)-(−)-α-phenylglycine, 875-74-1; DNP-(*R*)-(−)-α-phenylglycine, 6367-35-7; (*S*)-(−)-phenylalanine, 10549-09-4; DNP-(*S*)-(−)-phenylalanine, 10549-10-7; (*R*)-(+)-phenylalanine, 10549-11-8; DNP-(*R*)-(+)-phenylalanine, 10549-12-9; (*S*)-(+)-glutamic acid, 10549-13-0; DNP-(*S*)-(+)-glutamic acid, 10549-14-1; N-(*R*)-(+)-α-methylbenzylbenzoylformamide, 10549-15-2; N-(*S*)-(−)-α-methylbenzylbenzoylformamide, 10549-16-3; N-(*R*)-(+)-α-ethylbenzylbenzoylformamide, 10549-17-4; N-(*S*)-(−)-α-ethylbenzylbenzoylformamide, 10549-18-5; (*R*)-(−)-alanine isobutyl ester *p*-toluenesulfonate, 10549-19-6; (*S*)-(+)-alanine isobutyl ester *p*-toluenesulfonate, 10549-20-9; (*R*)-(−)-valine isobutyl ester *p*-toluenesulfonate, 13018-44-5; (*S*)-(+)-valine isobutyl ester *p*-toluenesulfonate, 13018-45-6; DNP-(*S*)-(+)-valine, 10549-21-0.

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The Reaction of Nitrous Acid with Some Glyoxylic Acids[1]

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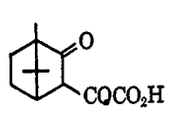
The product from the nitrosation of camphor-3-glyoxylic acid is shown to be 1,8,8-trimethyl-3-hydroxy-3-azabicyclo[3.2.1]octan-2-one-*exo*-4-carboxylic acid. β-Santenone-3-glyoxylic acid, but not the α isomer, undergoes an analogous rearrangement. The scope of the reaction is investigated, and a possible mechanism is described.

In the course of a study of the reactions of nitrous acid with various compounds, Chorley and Lapworth investigated the nitrosation of camphor-3-glyoxylic acid (**1**).[3] By analogy with the behavior of similar compounds, they anticipated the formation of either α-oximinocamphor (**2**) or the oximino acid **3**. A small amount of **2** was formed, but the major product was a water-soluble, crystalline acid, $C_{11}H_{17}NO_4$. Evolution of carbon dioxide was observed during the reaction, and the formation of the product was summarized by the equation, $C_{12}H_{16}O_4 + HNO_2 \rightarrow C_{11}H_{17}NO_4 + CO_2$.



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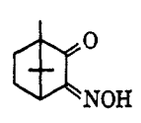

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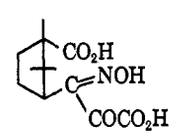

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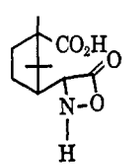
The new acid was monobasic, melted at 160° with loss of carbon dioxide, gave a red-violet color with ferric chloride, and showed remarkable resistance to hydrolysis by strong acids or bases. It exhibited no properties characteristic of aldehydes and ketones, and on oxidation gave camphoric acid (**5**). When the acid was refluxed with 50% aqueous potassium hydroxide, an isomeric acid was formed which had properties so similar to those of the parent acid that the acids were believed to be stereoisomers. Reduction of the parent acid with alkaline ferrous hydroxide gave an acid, $C_{11}H_{17}NO_3$, which had an indefinite melting point. This compound failed to give a ferric chloride test, and thermal decomposition of its silver salt gave α-camphidone (**8**). On this basis, the reduced acid was formulated as α-camphidonecarboxylic acid (**7**).

Methylation of the parent acid with dimethyl sulfate and alkali gave both a monomethyl and a dimethyl derivative. Neither of these derivatives gave a color with ferric chloride, and, whereas the monomethyl derivative expelled carbon dioxide from sodium bicarbonate, the dimethyl derivative was devoid of acidic properties. Treatment of the latter compound with alkali gave only ammonia and no methylamine, and it was concluded that both methyl groups were attached to oxygen.

Chorley and Lapworth, "after very long consideration" were forced to adopt **11** as the structure of the



11

acid. One of the premises from which they argued was that the molecule must contain an enolic grouping, $>C{=}C<^{OH}$ or $>N{=}C<^{OH}$ to account for the positive test with ferric chloride, and apparently they did not consider the possibility of a cyclic hydroxamic acid. Failure to consider this possibility has been noted previously,[4] and in fact the tentative structure suggested is the one which we conclude to be correct on the basis of our studies.

The product obtained by nitrosation of camphor-3-glyoxylic acid exhibited properties in agreement with those reported. Spectroscopic properties permit several conclusions about the structure. Infrared absorption bands are present at 3.12 (OH), 3.8 and 5.76 (carboxylic acid), and 6.20 μ (amide I). The nmr spectrum in dimethyl sulfoxide-d_6 shows methyl signals at τ 8.98, 9.03, and 9.13, and a two-proton hydroxyl peak at 2.33. A one-proton singlet (half-width = 4.0 cps)

(1) Taken from the Ph.D. Dissertation of L. D. Hatfield, Aug 1966.
(2) To whom inquiries should be addressed.
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