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Sulfinylamine Chemistry. I. A New Degradation Reaction of α-Amino Acid with N-Sulfinylaniline*,[1]

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Analogously to the Strecker degradation method, α-amino acids were converted to carbonyl derivatives by treatment with N-sulfinylaniline below 100° in dimethylsulfoxide (or benzene). The sodium salts prefer to the free acids as substrates (35—75% yield). In contrast with other α-amino acids, glycine was further oxidized to formic acid derivative. Also, α-amino acid ethyl esters were submitted to the same treatment and usually converted to keto acid esters as expected. However, the reaction of ethyl glycinate proceeded unordinarily to afford diethyl 1,2,5-thiadiazole-3,4-dicarboxylate. The degradation reaction pathway of α-amino acids was discussed with some evidences and speculations.

It has been well-known that the sulfinyl group of N-sulfinylaniline transfers to nitrogen of more basic amine *via* interchange by the equilibrium reaction.[3] This knowledge suggests that the reaction of α-amino acid with N-sulfinylaniline may proceed analogously to afford N-sulfino α-amino acid cyclic anhydride which contains the reactive carboxyl group. As a preliminary trial, reaction of DL-phenylglycine with N-sulfinylaniline[4] in dimethylsulfoxide (DMSO) was carried out by heating for a few hours expecting the formation of N-sulfino DL-phenylglycine cyclic anhydride (**1**) through the sulfinyl group transfer.[3] However, the reaction did not proceed in this manner and gave rise to the oxidative degradation affording benzylideneaniline (**2**) (Chart 1).

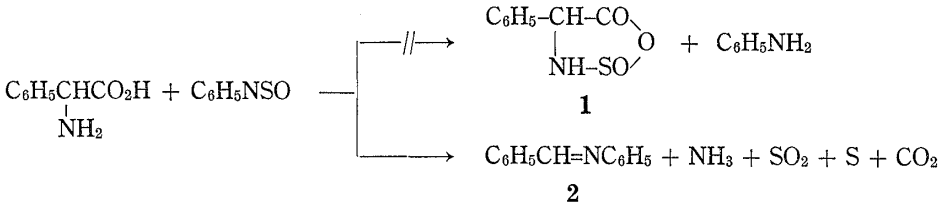

Chart 1

This observation prompted us to investigate reactions of several α-amino acids with N-sulfinylaniline for developing a new method of their degradation. The reactions were carried out in anhydrous DMSO and afforded usually carbonyl derivatives. Table I shows α-amino acids treated, reaction conditions and results. The results-indicate that the sodium salts prefer to the free acids as substrates. This may be caused because the sulfinyl group transfers from N-sulfinylaniline easier to the sodium salts than to the free acids under the government of basicity

* Dedicated to the memory of Prof. Eiji Ochiai

1) This study was presented at the 95th Annual Meeting of the Pharmaceutical Society of Japan, Nishinomiya, April, 1975.

2) Location: *Maedashi-3-chome, Higashi-ku, Fukuoka, 812, Japan.*

3) *a*) G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H.P. Patzschke, H. Smalla and A. Trede, *Angew. Chem.*, **74**, 135 (1962); *b*) G. Kresze and W. Wucherpfenig, *Angew. Chem.*, **79**, 109 (1967); *c*) O. Tsuge and S. Mataka, *Yuki Gosei Kagaku Kyokai Shi*, **29**, 933 (1971).

4) *a*) A. Michaelis and R. Herz, *Chem. Ber.*, **23**, 3480 (1890); *b*) P. Rajagopalan, B.G. Advani and C.N. Talaty ,"Organic Syntheses," Coll. Vol. V, John Wiley & Sons, Inc., New York, N.Y., 1973, p. 504.

Table I. Reactions of α-Amino Acids with N-Sulfinylaniline (an equimole) in DMSO

$\begin{matrix}R\\R'\end{matrix}\!\!>\!C(NH_2)\text{-}CO_2M$			Reaction		Product	Yield (%)
R	R′	M	Temp. (°C)	hr		
H	H	H	80	1	$C_6H_5N=CHNHC_6H_5$[5]	9
H	H	Na	80	1		35
DL CH_3	H	Na	room temp.	6	CH_3CHO[a]	72
DL $(CH_3)_2CH$	H	H	room temp.	6		24
DL $(CH_3)_2CH$	H	Na	room temp.	6		54
L $(CH_3)_2CH$	H	H	room temp.	6	$(CH_3)_2CHCHO$[b]	25
L $(CH_3)_2CH$	H	Na	room temp.	6		49
DL C_6H_5	H	H	80	4		57
DL C_6H_5	H	Na	room temp.	4	$C_6H_5CH=NC_6H_5$[7]	76
DL C_6H_5	CH_3	Na	100	10	$\begin{matrix}C_6H_5\\CH_3\end{matrix}\!\!>\!C=NC_6H_5$[8]	72

a) dimethon : mp 142—143° (ethanol)[6]
b) dimethon : mp 154° (ethanol)[6]

strength. Among α-amino acids treated, glycine differed from others in the sense that it was oxidized further to N,N′-diphenylformamidine[5] over the carbonyl derivative. Thus, this procedure can be used as a new tool in the Strecker degradation reaction[9] because it is furnished with mild reaction condition, easy operation and comparative good yield.

Also, the reaction of α-amino acid esters with N-sulfinylaniline was examined in various solvents. As expected, the treatment of ethyl DL-phenylglycinate gave ethyl benzoylfor-

Table II. Reactions of α-Amino Acid Esters with N-Sulfinylaniline in Anhydrous Aprotic Solvent

Ester	Reaction		Solvent	Product	Yield (%)
	Temp. (°C)	hr			
DL $C_6H_5CH(NH_2)CO_2C_2H_5$	80	2	DMSO	$C_6H_5COCO_2C_2H_5$[a]	31
	reflux	2	benzene		29
$CH_2(NH_2)CO_2C_2H_5$	80	2	DMSO	$H_5C_2O_2C-C(=N)-C(=N)-CO_2C_2H_5$ (N–S–N)[b]	24
	reflux	2	benzene or ether		30

a) bp 138°/12 mmHg. 2,4-Dinitrophenylhydrazone, mp 136° (ethanol)[10].
b) dimethon: bp 97°/3 mmHg[11].

5) J.B. Shoesmith and J. Halane, *J. Chem. Soc.*, **125**, 2705 (1924).
6) E.C. Horning and M.G. Horning, *J. Org. Chem.*, **11**, 95 (1946).
7) L.A. Bigelow and H. Eatough, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons Inc., New York, N.Y., 1948, p. 80.
8) J. Hoch, *Compt. Rend.*, **199**, 1428 (1934).
9) A. Schönberg and R. Houbacher, *Chem. Rev.*, **50**, 261 (1952).

mate.[10] However, the same treatment of ethyl glycinate exhibited an unusual result affording diethyl 1,2,5-thiadiazole-3,4-dicarboxylate[11] (Table II).

Like the case of α-amino acids, aliphatic primary amines were converted to carbonyl derivatives *via* the oxidative deamination by the treatment with N-sulfinylaniline, suggesting that the reaction pathways may be analogous between both series of compounds. Though whole aspect of these results will be reported in the subsequent paper, we quote some from these results because they help the discussion of the reaction pathway of α-amino acid degradation. For the oxidative degradation, N-sulfinylaniline is supposed to work on α-amino acid through either of three most probable ways, A, B and C (Chart 2). This supposition is based on judging from the chemical behaviors of N-sulfinylaniline which have been already made clear and from the fact that the reaction is usually accompanied with by-productions of sulfur dioxide and sulfur.

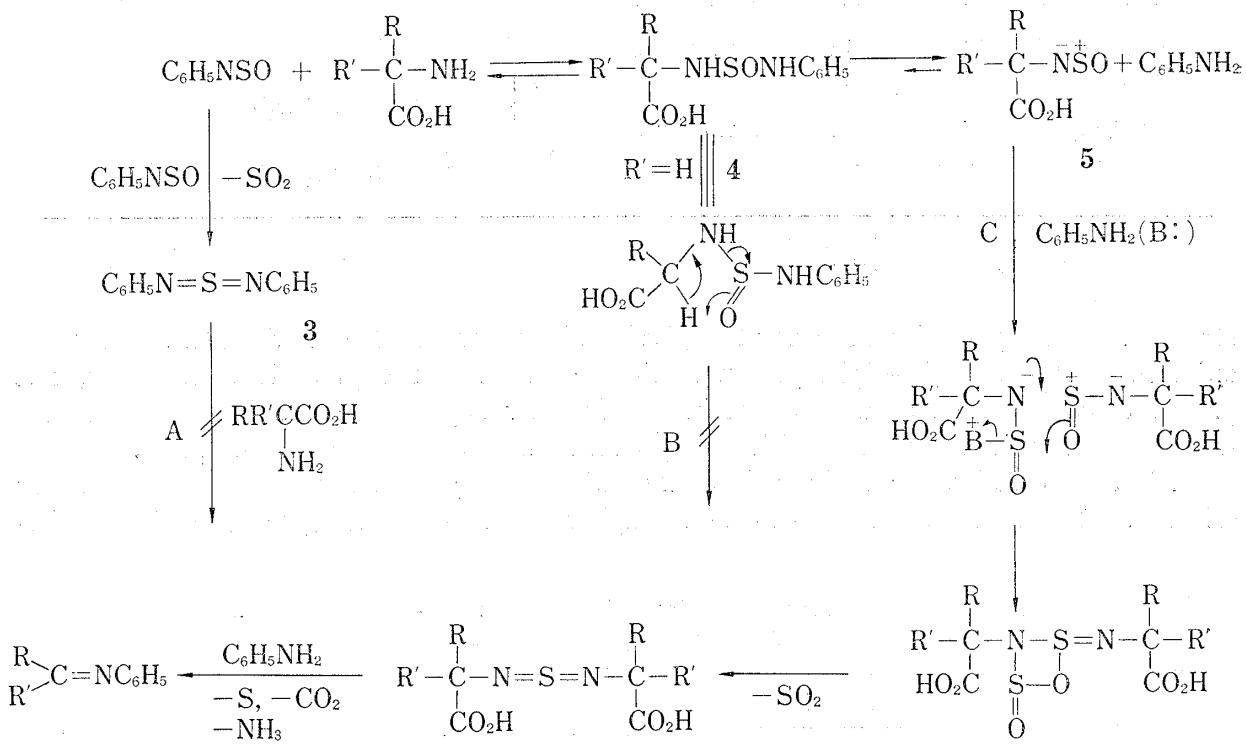

Chart 2

Pathway A: N-Sulfinylaniline transforms in the presence of base to N,N′-diphenylsulfurdiimine (3)[12] which may act as oxidizing agent to bring α-amino acid to carbonyl derivative. As a trial, isobutylamine was treated with the sulfurdiimine (3)[12] in DMSO at 80° for one hour. However, this attempt did not afford isobutyraldehyde but 2-(N-phenylsulfenamoyl)-isobutyraldehyde (8) (Chart 3). Thus, this pathway is excluded.

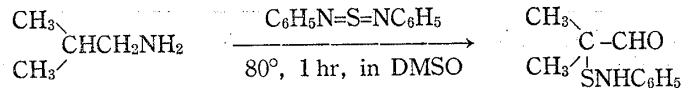

Chart 3

10) B.B. Corson, R.A. Dodge, S.A. Harris and R.K. Hazen, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N.Y., 1948, p. 241.
11) I. Sekikawa, *Bull. Chem. Soc. Japan*, 33, 1229 (1960).
12) H.H. Hörhold and J. Beck, *J. Prakt. Chem.*, 311, 621 (1969).

Pathway B: On the way of reaction where the sulfinyl group transfers from aniline to α-amino acid, it passes through the intermediate (**4**). The oxidative degradation reaction may be supposed to occur *via* the decomposition of this intermediate as shown in Chart 2. However, it denies this route that the degradation reaction of DL-2-amino-2-phenylpropionic acid (Table I) can not be explained by this route.

Pathway C: The sulfinyl group of N-sulfinylaniline transfers to α-amino acid[3] to produce **5** *via* which the degradation may occur. To prove the possibility of this route, the following experiments were made. Isobutylamine was treated with N-sulfinylaniline in cold ether producing N-sulfinylisobutylamine (**9**)[13] in 24% yield.

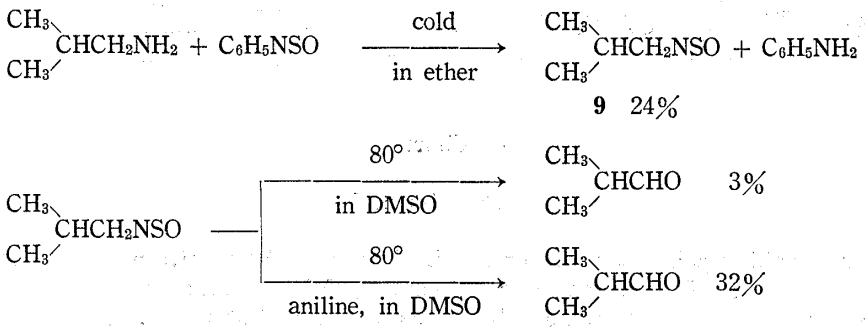

Chart 4

Heating of **9** in DMSO at 80° afforded no isobutyraldehyde more than trace (3% yield). But addition of aniline to the reaction mixture facilitated the oxidative deamination markedly to improve yield of isobutyraldehyde (Chart 4). This suggests that the deamination easily occurs *via* **5** and aniline plays some role in the reaction. Though steps after **5** are not clear, the formation of diethyl 1,2,5-thiadiazole-3,4-dicarboxylate from ethyl glycinate (Chart 6) gives some bases to the speculation of reaction course which involves the sulfurdiimine (**6**) as an intermediate: The carbonyl derivative (**7**) is produced by the action of aniline on the sulfurdiimine (**6**) which is formed by dimerization of **5** followed by elimination of sulfur dioxide. Moreover, the explanation agrees with experimental observation that sulfur dioxide and sulfur are produced in the course. However, as chemical properties of aliphatic sulfurdiimine have not been made clear, there remain some doubts about the explanation which should be resolved in future. The formation of N,N′-diphenylformamidine from glycine in reaction with N-sulfinylaniline (Table I) is speculatively interpreted as shown in Chart 5: That is, aniline adds to the initial degradation product (methyleneimine) and the resulting N-phenylmethylenediamine suffers again the action of N-sulfinylaniline to produce N,N′-phenylformamidine.

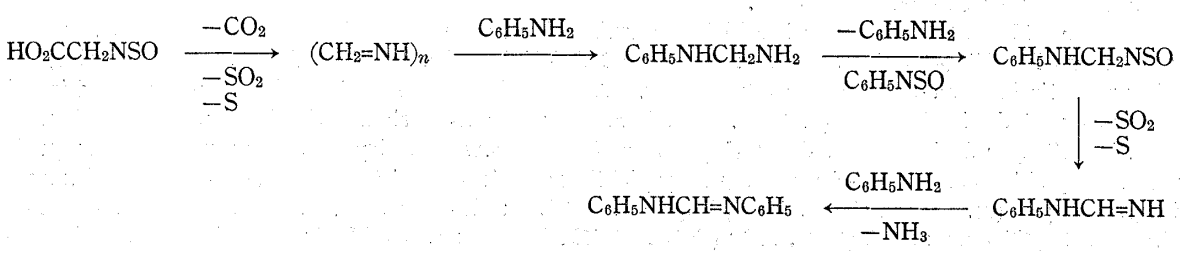

Chart 5

The unusual reaction where diethyl 1,2,5-thiadiazole-3,4-dicarboxylate was formed from ethyl glycinate (Table II) was presumably interpreted as passing through b (Chart 6). This interpretation stands just on the reference of the report that reaction of benzyl phenyl ketone with thionyl chloride produces the olefin derivative *via* sulphine (**10**) and the thiirane (**11**)

13) D. Klamann, C. Sass and M. Zelenka, *Chem. Ber.*, **92**, 1910 (1959).

intermediates[14] (Chart 6, a). An effort is being paid to provide direct evidences for the mechanistic interpretation of the above both cases.

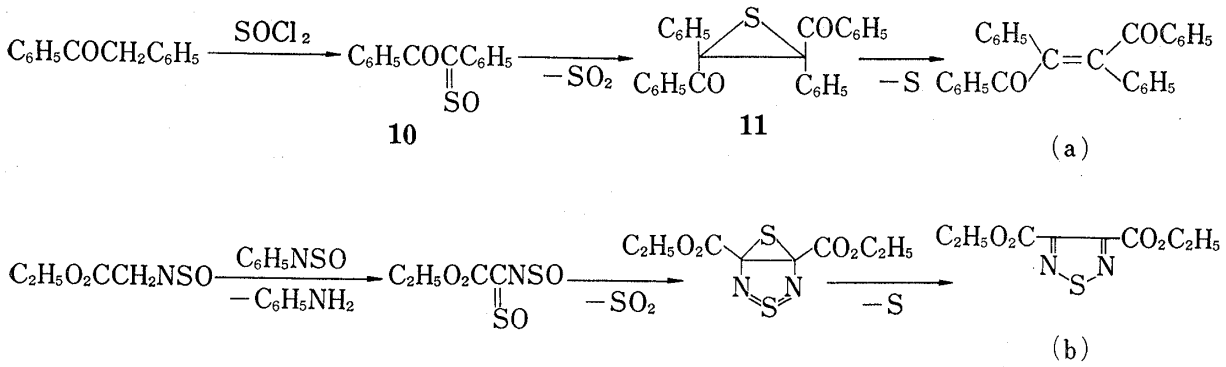

Chart 6

Experimental

All melting and boiling points were uncorrected. Infrared (IR) spectra were recorded with a JASCO IRA-1 Spectrophotometer. Nuclear magnetic resonance (NMR) spectrum was obtained in CCl_4 with a JOEL DS-100 spectrometer using tetramethylsilane as an internal standard. Mass spectrum was determined on a JEOL JMS-OISG spectrometer. The identifications of all products were carried out by mixed melting point determinations and comparisons of IR spectra with authentic samples.

Materials——N-Sulfinylaniline,[4] N,N′-diphenylsulfurdiimine,[12] DL-2-amino-2-phenylpropionic acid,[15] ethyl glycinate,[16] ethyl DL-2-phenylglycinate[17] and sodium salts of α-amino acids[18] were prepared by the methods described in literatures. Other starting materials were obtained commercially.

Reactions of α-Amino Acids and Their Sodium Salts with N-Sulfinylaniline——General Procedure: To α-amino acid or its sodium salt (50 mmoles) in anhydrous DMSO (40 ml) was added dropwise N-sulfinylaniline (50 mmoles) while stirring and then stirring was continued for 30 min. The mixture was further kept at room temperature —100° for 1—10 hr while stirring. The reaction mixture was poured into ice-H_2O (100 ml). The subsequent operations were carried out in two ways. 1) In the case of glycine, DL-2-phenylglycine, DL-2-amino-2-phenylpropionic acid and their sodium salts: The mixture was extracted with benzene (100 ml) and the benzene layer was washed with H_2O, 10% aq. HCl solution, 5% aq. $NaHCO_3$ solution and then H_2O, dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue (anil compound) was purified by recrystallization. 2) In the case of DL-alanine, DL- and L-valine and their sodium salts: The mixture was steam-distilled until the distillate reached to 40 ml. This operation caused hydrolysis of the product (anil) to the aldehyde which was characterized as the dimethone derivative. Reaction conditions and results were recorded in Table I.

Reactions of α-Amino Acid Ethyl Esters with N-Sulfinylaniline——The reaction of α-amino acid ethyl ester (50 mmoles) with N-sulfinylaniline (50 mmoles) in anhydrous solvent (DMSO, benzene or ether, 40 ml) was carried out just as in the case of the free acid. The product was isolated from the reaction mixture by extraction with benzene and purified by distillation under reduced pressure. Substrates, reaction conditions and results were listed in Table II.

Reaction of Isobutylamine with N,N′-Diphenylsulfurdiimine (3)——To isobutylamine (5.1 g, 70 mmoles) in anhydrous DMSO (40 ml) was added dropwise N,N′-diphenylsulfurdiimine[12] (7.5 g, 35 mmoles) while stirring and stirring was continued at 80° for 1 hr. After cooling, the reaction mixture was poured into ice-H_2O and extracted with benzene (100 ml). The benzene layer was washed with 10% aq. HCl solution, H_2O, 5% aq. $NaHCO_3$ and then H_2O, dried ($MgSO_4$) and evaporated to dryness. The residue was purified repeatedly by silica gel column-chromatography yielding a yellowish oil (3.4 g) of 2-(N-phenylsulfenamoyl)-isobutyraldehyde (**8**). *Anal.* Calcd. for $C_{10}H_{13}ONS$: C, 61.51; H, 6.71; N, 7.15. Found: C, 61.04; H, 6.50; N, 6.85. IR ν_{max}^{Nujol} cm^{-1}: 3380 (NH), 1720 (C=O). NMR (CCl_4) δ: 1.24 (6H, singlet, CH_3), 4.92 (1H, singlet, NH), 6.68—7.32 (5H, multiplet, C_6H_5). Mass Spectrum *m/e*: 195 (M^+).

14) C.J. Ireland and J.S. Pizey, *J. C. S. Chem. Commun.*, **1972**, 4.
15) R.E. Steiger, "Organic Syntheses," Coll. Vol. III, ed. by E.C. Horning, John Wiley & Sons, Inc., New York, N.Y., 1955, p. 88.
16) C.S. Marvel, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley & Sons, Inc., New York, N.Y., 1948, p. 310.
17) A. Kossel, *Chem. Ber.*, **24**, 4145 (1891).
18) M.M. Weizmann and L. Haskelberg, *Compt. Rend.*, **189**, 104 (1929).

N-Sulfinylisobutylamine——To isobutylamine (14.6 g, 200 mmoles) in ether (100 ml) was added dropwise an ethereal solution (50 ml) of N-sulfinylaniline (27.8 g, 200 mmoles) at room temperature for 30 min. The ether solution was evaporated to dryness and the residue was distilled *in vacuo* to afford a yellowish oil (5.7 g), 24% yield, bp 45° (50 mmHg) which was identical with an authentic sample[19] in comparison of IR spectra.

Thermal Treatment of N-Sulfinylisobutylamine——a) N-Sulfinylisobutylamine (3.3 g, 25 mmoles) was dissolved in DMSO (10 ml) and the solution was heated at 80° for 3 hr. After cooling, to the solution was added H_2O (50 ml) and steam-distilled until the distillate reached to 20 ml. To the distillate was added dimedone (7.0 g) dissolved in 50% ethanol and the precipitating dimethone was collected by filtration and recrystallized from 90% ethanol affording isobutyraldehyde dimethone (0.25 g), 3% yield, mp 154° alone and on admixture with an authentic sample,[6] b) N-Sulfinylisobutylamine (3.3 g, 25 mmoles) and aniline (2.3 g, 25 mmoles) was dissolved in DMSO (10 ml) and the solution was treated just as (a) affording the isobutyraldehyde dimethone (2.7 g), 32% yield.

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19) A. Michaelis and O. Storbeck, *Ann. Chem.*, **274**, 191 (1893).