Tetrahedron Letters No.12, pp. 1501-1506, 1968. Pergamon Press. Printed in Great Britain.

DETERMINATION OF THE ABSOLUTE CONFIGURATION OF MERCAPTOSUCCINIC ACID BY CHEMICAL CORRELATION WITH GLYCERALDEHYDE

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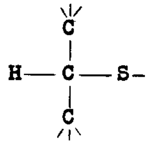
(Received in Japan 18 October 1967)

Compounds of type I which carry sulfur at the asymmetric carbon, have been synthesized or found in natural products.1) The absolute configuration of this type of compounds is either tentative or still unknown except for biotin,2) whose absolute configuration was recently determined by the X-ray fluorescence method.


(I)

For the configurational standard of these compounds (I), mercaptosuccinic acid seems to be most suitable, as glyceraldehyde in a series of carbohydrates. Fredga3) has deduced the absolute configuration of mercaptosuccinic acid by means of the method of quasi-racemates.

Direct chemical correlation of mercaptosuccinic acid with glyceraldehyde seems to be impossible, because the replacement of the C-S bond of mercaptosuccinic acid to the C-O bond is inevitable in the correlation between them. Some devices are required to correlate mercaptosuccinic acid with glyceraldehyde chemically, without effecting the bonds on the asymmetric carbon.

In the present communication, we wish to report the direct chemical correlation of optically active mercaptosuccinic acid with glyceraldehyde by way of (-)-VI, whose absolute configuration is clearly correlated to L-proline.[4)]

The reaction of (-)N-acetyl-4-p-tolylsulfonyloxy-L-proline methyl ester ((-)-III)[5) 6)] prepared from L-(-)-hydroxyproline((-)-II), with sodium benzylmercaptide in methanol gave the 4-benzylthio derivative(IV) as an oily substance. Hydrolysis of IV with an equimolar amount of sodium hydroxide in aqueous methanol followed by debenzylation with sodium in liquid ammonia afforded 4-mercapto derivative(V), which was converted to the thiolactone ((-)-VI), b.p$_{0.08}$ 142°, $[\alpha]_D^{24}$-114°($CHCl_3$), with N,N-dicyclohexylcarbodiimide in acetonitrile. Mass spectral data and molecular weight measurements proved this to be monomer (-)-VI, not the dimer nor the polymer. Esterification and S-methylation of (-)-VI with diazomethane,[7)] in a mixture of methanol and ether, afforded (-)-VII, b.p$_{0.06}$ 156-7°, $[\alpha]_D^{25}$-47.3°(MeOH). Hydrolysis of (-)-VII with dilute hydrochloric acid, and treatment with Amberlite IR-120, gave the amino acid((-)-VIII),[8)] m.p.242°(decomp.), $[\alpha]_D^{28}$-60.8°(H_2O). Periodate oxidation[9)] of (-)-VIII, followed by further oxidation with potassium permanganate,[10)] yielded the (-)-sulfonyl lactam((-)-IX), m.p.167-9°(decomp.), $[\alpha]_D^{28}$-28.5°(C=0.604, MeOH). Acetylation of (-)-VIII with acetic anhydride in acetic acid and desulfurization with Raney nickel yielded (-)N-acetyl-L-proline((-)-X).[11)] Therefore, the absolute configuration of the carbon bearing carbonyl group of (-)-VI has been demonstrated to be S (L-series), subsequently the absolute configuration of (-)-IX has been proved to be S through (-)-VI, as shown in chart I.

In order to correlate the sulfonyl lactam((-)-IX), whose absolute configuration was thus established, with mercaptosuccinic acid(XVIII) the following chemical sequence was attempted as shown in chart II. According to the reported method,[12)] L-(-)-asparagine((-)-XI) was converted to (-)-2-bromosuccinamic acid((-)-XII),[13)] the reaction of which, with sodium methylmercaptide, gave a methylthio derivative((+)-XIII), m.p.138-140°, $[\alpha]_D^{8}$+113° (MeOH). Esterification of (+)-XIII with diazomethane and subsequent treatment with an equimolar amount of sodium hydroxide[14)] in cold aqueous methanol afforded the imide((+)-XV), m.p.52.5-54.5°, $[\alpha]_D^{27}$+63.7°(MeOH). Partial

CHART I

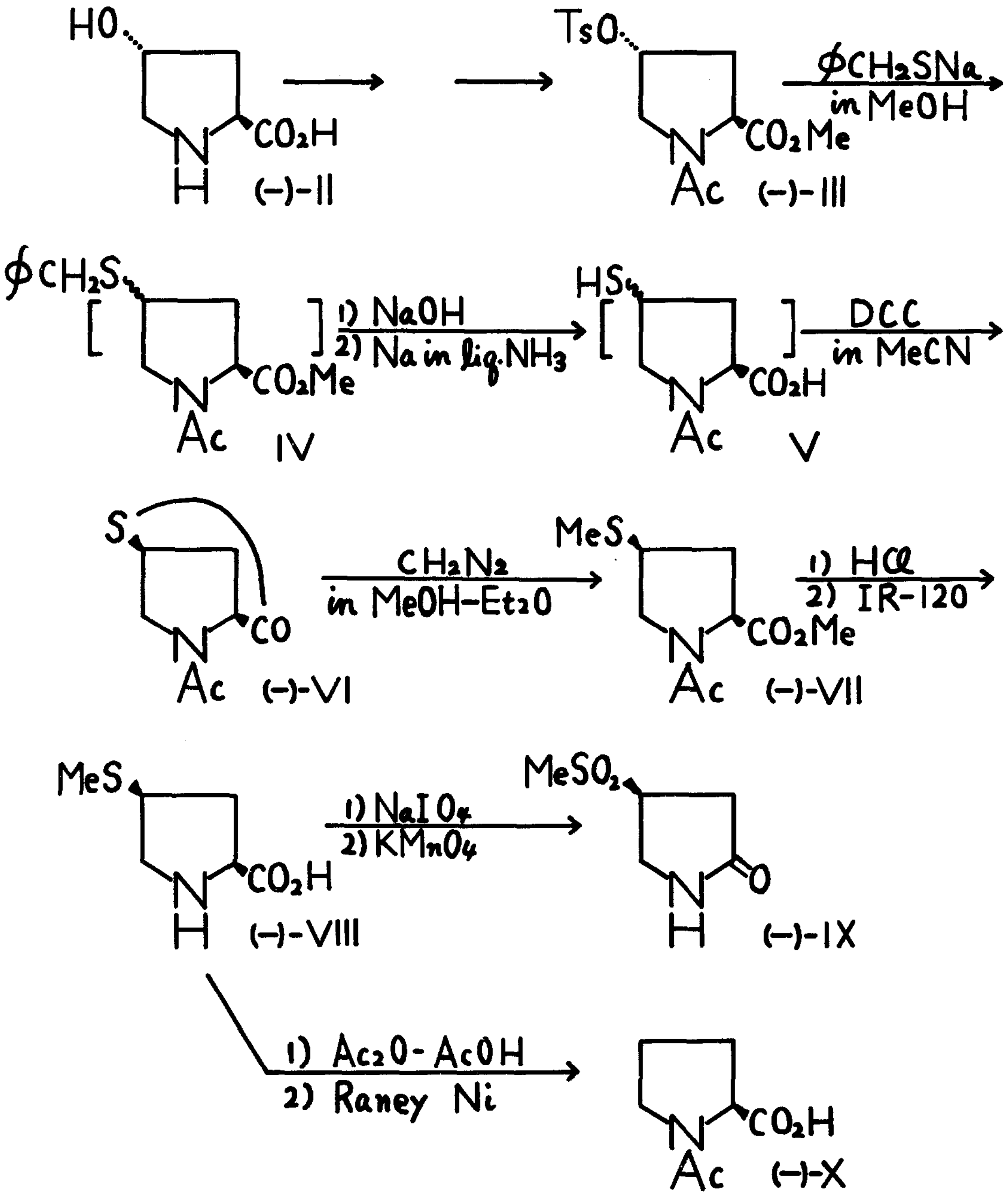
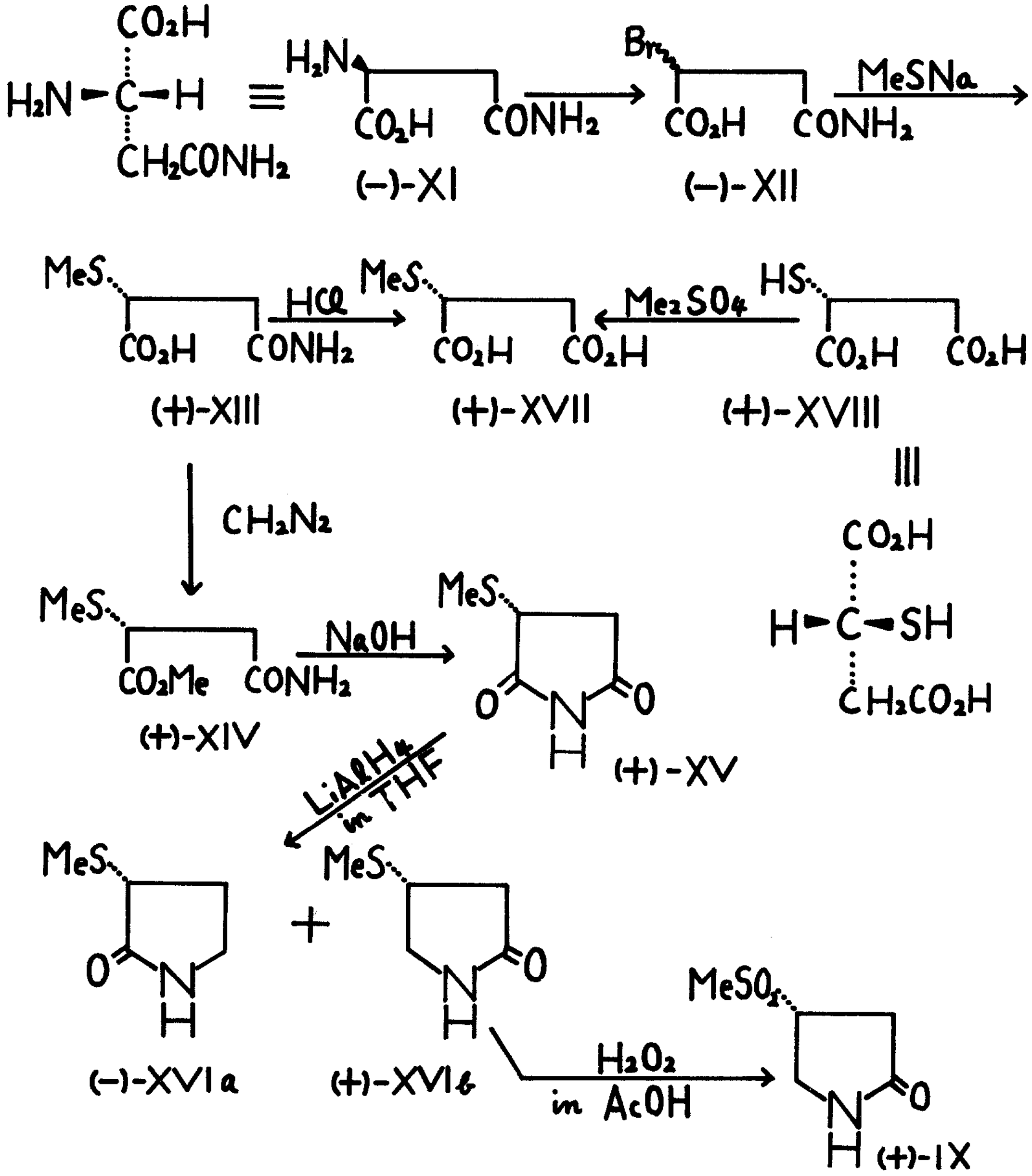

HO
CO₂H
N
H
(−)-II
TsO
CO₂Me
Ac
(−)-III
ϕCH₂SNa
in MeOH
ϕCH₂S
CO₂Me
IV
1) NaOH
2) Na in liq. NH₃
HS
CO₂H
V
DCC
in MeCN
S
CO
(−)-VI
CH₂N₂
in MeOH-Et₂O
MeS
CO₂Me
(−)-VII
1) HCl
2) IR-120
MeS
CO₂H
(−)-VIII
1) NaIO₄
2) KMnO₄
MeSO₂
O
(−)-IX
1) Ac₂O-AcOH
2) Raney Ni
CO₂H
(−)-X

CHART II


(−)-XI
(−)-XII
MeSNa
(+)-XIII
HCl
(+)-XVII
Me₂SO₄
(+)-XVIII
CH₂N₂
(+)-XIV
NaOH
(+)-XV
LiAlH₄ in THF
(−)-XVIa
(+)-XVIb
H₂O₂ in AcOH
(+)-IX

reduction of (+)-XV with a calculated amount of lithium aluminum hydride (about 0.75 molar equivalent) in tetrahydrofuran afforded a reaction mixture containing lactams ((-)-XVIa) and ((+)-XVIb).

Separation of isomers, (-)-XVIa and (+)-XVIb, from the mixture was successful by means of column chromatography on silica gel with 5% ethanol in benzene. Oxidation of (+)-XVIb by hydrogen peroxide in acetic acid afforded (+)-sulfonyl lactam((+)-IX), m.p. 167-8°(decomp.), $[\alpha]_D^{27}$ +26.8°(C=0.606, MeOH). The infrared spectrum(KBr) of (+)-IX was superimposable with that(KBr) of (-)-IX and the optical rotatory dispersion curve of (-)-IX was antipodal to that of (+)-IX. Hydrolysis of (+)-XIII with dilute hydrochloric acid afforded (+)-XVII.15) S-Methylation of (+)-XVIII16) with dimethylsulfate gave the same (+)-methylsulfide((+)-XVII).

Accordingly, the absolute configuration of (+)-mercaptosuccinic acid ((+)-XVIII) has thus been elucidated to be R, as shown in chart II, based on the correlation of mercaptosuccinic acid with glyceraldehyde via L-proline. Fortunately, Fredga's proposal agreed with our demonstration.

Satisfactory analytical data have been obtained for all new compounds except those in brackets.

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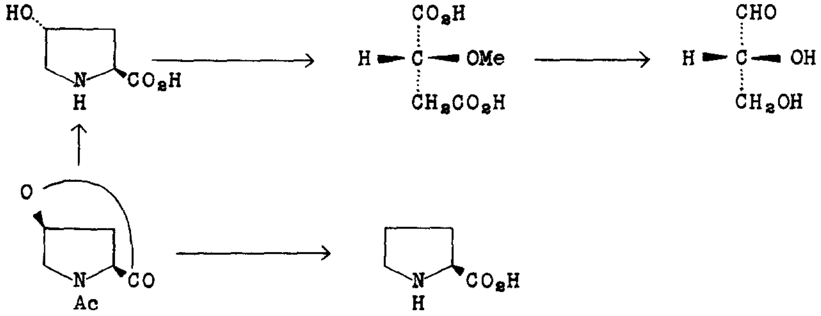

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