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N-Quaternary Compounds

Part XIX. The Menschutkin Reaction

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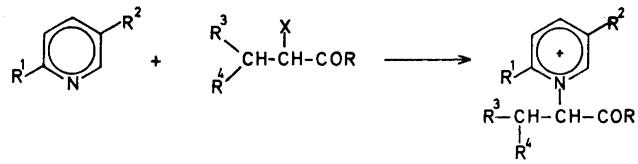
Alkylation of 3-hydroxypyridine with optically active alkanoic acids carrying a displaceable substituent on the α-carbon has been studied in the solvents toluene, acetonitrile, and DMF. The reaction rate and the optical yield was highest in toluene. An explanation is given. The reaction rate was increased by a β-thioether group in the alkylating agent. For esters and amides the reaction rate was markedly reduced.

The reactions with α-bromo acids proceeded by inversion of the configuration except in a case with branching on the β-carbon where the configuration was retained. Configurational retention was found for α-tosyloxypropionic acid.

Esters gave net inversion of the configuration, but with high degree of racemisation. The highest optical yield was obtained in the absence of a solvent. The amide of α-bromopropionic acid was not optically stable enough for stereochemical studies.

Possible racemisation modes of the optically active reagents and condensation products have been studied.

Rate studies of the Menschutkin reaction between an alkyl halide and a pyridine base show second order kinetics.[1] Variations in the alkyl group R and the leaving group X in RX follow the usual behaviour of RX towards nucleophiles.[2] With tertiary halides elimination of hydrogen halide and olefin formation is the dominant pathway.[2] A report on the quaternisation at chiral carbon shows that an optically active product is formed.[3] The main interest in the Menschutkin reaction has been restricted to rate studies on the influence of solvents and electronic and steric effects.[1,2,4,5] In connection with our studies of pyridinium-3-oxide derivatives [6,7] we became interested in the reaction between derivatives of α-substituted carboxylic acid and 3-hydroxypyridines. The steric course of this reaction has been studied using optically active acid derivatives, but no kinetic measurements have been carried out. The configuration of the condensation products could be assigned by optical rotation comparisons with the same products prepared from amino acids of known configuration in such a way that the configuration at the asymmetric carbon was not affected.[8,9]



I II – VIII IX – XI

Scheme 1.

I a $R^1=R^2=H$
b $R^1=H$, $R^2=OH$
c $R^1=CH_3$, $R^2=OH$

II a $R^3=R^4=H$, $R=OH$, $X=Br$
b $R^3=R^4=H$, $R=OH$, $X=I$
c $R^3=R^4=H$, $R=OH$, $X=OSO_2C_6H_4CH_3$

III $R^3=R^4=CH_3$, $R=OH$, $X=Br$

IV $R^3=H$, $R^4=C_6H_5$, $R=OH$, $X=Br$

V $R^3=H$, $R^4=CH_2SCH_3$, $R=OH$, $X=Br$

VI $R^3=H$, $R^4=SCH_2C_6H_5$, $R=OH$, $X=Br$

VII a $R^3=R^4=H$, $R=OC_2H_5$, $X=Br$
b $R^3=R^4=H$, $R=OC_2H_5$, $X=OSO_2C_6H_4CH_3$

VIII $R^3=R^4=H$, $X=Br$, $R=N(CH_3)_2$

IX a $R^1=H$, $R^2=OH$, $R^3=R^4=H$, $R=OH$
b $R^1=CH_3$, $R^2=OH$, $R^3=R^4=H$, $R=OH$
c $R^1=H$, $R^2=OH$, $R^3=R^4=CH_3$, $R=OH$
d $R^1=H$, $R^2=OH$, $R^3=H$, $R^4=C_6H_5$, $R=OH$
e $R^1=H$, $R^2=OH$, $R^3=H$, $R^4=CH_2SCH_3$, $R=OH$

X a $R^1=H$, $R^2=OH$, $R^3=R^4=H$, $R=OC_2H_5$
b $R^1=R^2=R^3=R^4=H$, $R=OC_2H_5$

XI $R^1=H$, $R^2=OH$, $R^3=R^4=H$, $R=N(CH_3)_2$

The relative importance of neighbouring group participation in acids was studied through variations of the substituents R^3, R^4, and X (II – VI). Two esters and one amide (VII – VIII) were also studied. The alkylations were found to occur exclusively on the annular nitrogen. Previously we have established that *O*-alkylation only becomes important when the pyridine carries a bulky *ortho* substituent while the smaller methyl group does not prevent preferential *N*-alkylation.[7] The low nucleophilicity of the annular nitrogen makes necessary fairly vigorous reaction conditions so that substantial amounts of byproducts are formed and the acid IX is readily decarboxylated because of the quaternary nitrogen activation. Polar solvents such as DMA, DMF, MeOH, and acetonitrile should lower the activation energy by the solvation of the transition state where a net charge increase is assumed. However, toluene was the best solvent. In the case of esters the alkylating agent itself was a good solvent. The relative rates of the reaction could be qualitatively determined at 80°. Below 50° the reaction was too slow and above 100° byproducts dominated, especially in DMA and DMF. The concentrations of the reactants were about 10^{-2} mol/50 ml solvent and the reaction time varied from 5 min for the fastest acid to 3 days for the slowest ester. As leaving groups were used Br, I, and OTos.

The pyridinium derivatives of carboxylic acids were isolated as zwitterions from their salts in ethanol-ether solution. The acid salt is in equilibrium with the zwitterion and the acid, and the former is gradually precipitated due to low solubility. Alternatively, the zwitterion was isolated by passing a solution of the salt through a DEAE-Sephadex column in the amine form. The pyridinium derivatives of the esters and the amide were isolated as salts.

The optically active 2-bromocarboxylic acids were prepared from optically active amino acids by diazotisation in the presence of bromide ions.[10–14] The reaction goes with retention of configuration and the optical purity is of the order of 90 %, somewhat dependent on the nature of the substituents. Optically active α-iodopropionic acid is not available directly from optically active precursors by iodide substitution since racemisation occurs readily by interchange of iodide ions. Therefore L-iodopropionic acid was obtained from the DL-modification by resolution with L-phenethylamine,[15] and the optical purity was 90 %. Tosylation of ethyl L-lactate furnished ethyl L-2-tosyloxypropionate in which the ethyl ester group was selectively hydrolyzed with $Ba(OH)_2$.[16] Treatment of L-2-bromopropionyl chloride with dimethylamine in ether yielded *N*,*N*-dimethyl-2-bromopropionamide,[17] but the amide was not sufficiently optically stable for the preparation of active pyridinium derivatives.

Since toluene is the best solvent, and the reaction rate does not increase with increase in the polarity of the solvents, first order reactions are excluded. Second order irreversible reactions, however, should also be accelerated by increase in polarity, since the reagents are non-charged and there is a net charge increase in the transition state. The reason for this abnormal behaviour must be sought in the nature of the reactants. Simple carboxylic acids are well known to be dimeric in non-polar solvents. The 2-substituted carboxylic acids can also be assumed to exist in a dimeric form in toluene. The polar dimeric forms could come together in larger aggregates. 3-Hydroxypyridine is not readily soluble in toluene, not even at the reaction temperature of 80°. The solubility, however, is markedly increased in the presence of the above acids. One therefore can assume that the pyridinol is dissolved in the aggregates of the acid, and that the alkylation actually takes place in these polar aggregates where favourable conditions exist for stabilization of the transition state. The esters and the amide should show less tendency for aggregate formation, and were found to react more slowly. The reaction conditions in toluene would be similar to carrying out the reaction with the alkylating agent as a solvent and reagent. For the ester (X) such reactions were found to be much faster and the optical purity very much higher.

A parallel to the above findings comes from the observation [18] that alcoholysis of triphenylchloromethane proceeded readily according to an S_N1 mechanism in carbon tetrachloride despite the unpolar solvent. The explanation offered was that ethanol in carbon tetrachloride exists as a trimer and that the reaction proceeded as if ethanol were the solvent.

With pyridine instead of pyridinol as the nucleophile in toluene the reaction rate was much decreased. This agrees well with the above explanation since pyridine is readily soluble in toluene and this decreases the tendency for the pyridine molecule to seek contact with the polar aggregates of the alkylating agent. Finally it should be pointed out that in the reported kinetic

studies of the Menschutkin reaction, nucleophiles such as pyridine and alkylpyridines [1,4,5] were used together with bromo or iodo alkanes. These reagents are all lipophilic and the expected increase in reaction rate with polarity of the solvent used is observed.

The products obtained are racemised to various degrees. Some understanding of the factors affecting the rate of racemisation is available from studies in aqueous alkali.[19] Thus 2-(3-hydroxy-6-methylpyridinium)propionate in N NaOH at 40° is fully racemised in 3 h. The ease of racemisation is due to activation of the chiral proton by the quaternary nitrogen. It seemed that unreacted pyridine could also act as a base during the reaction since the optical yield was higher with excess alkylating agent. This was confirmed by heating ethyl D-2-(3-hydroxypyridinium)propionate *p*-toluene-sulphonate (Xa) with 3-hydroxypyridine in acetonitrile at 80°. The optical rotation was reduced to 45 % in the course of one hour. In the absence of 3-hydroxypyridine the rotation was unchanged.

Racemisation by nucleophilic interchange of the pyridinol nucleus was ruled out, by heating the above ester with pyridine in acetonitrile. The optical activity was reduced by 30 %, but it was not possible to detect any liberated 3-pyridinol by chromatography. That the pyridine nucleus is a poor leaving group also follows from the fact that the anions I^-, Br^- do not displace the pyridine from the quaternary products as shown by the unchanged specific rotation of 2-(3-hydroxy-pyridinium)propionic acid after heating at 100° in aqueous HI, or in general by acid hydrolysis of esters.

Racemisation of the alkylating agent can well be responsible for the low optical purity of some of the products. Thus Hannerz [15] has shown that optically active iodopropionic acid is fully racemised in the course of 9 h in aqueous KI at room temperature. We obtained a nearly racemic product from iodopropionic acid (Table 1). When active 2-bromopropionic acid was heated with HBr in acetonitrile at 80° for 1 h, the specific rotation was reduced by 77 %. A similar experiment with ethyl 2-tosyloxypropionate and *p*-toluene-sulphonic acid salt, however, did not lead to any change in the specific rotation. The tosyloxy group is known to be a poor nucleophile in agreement with the above result, and this in part explains the relatively high optical yield in these reactions. Also the large degree of racemisation encountered after prolonged reaction times with bromo and iodo acids and esters is largely due to racemisation of the alkylating agent.

A reaction time of more than 2 – 3 h in the condensation leads to complete racemisation. With the racemisation experiments in mind, however, it is possible to extrapolate the reaction time back to zero in which case Table 1 gives a good idea of the mechanism in operation in each case. Thus the reaction between L-bromopropionic acid and 3-hydroxypyridine leads to inversion of the configuration. L-Iodopropionic acid appears to give some net retention. L-Tosyloxypropionic acid reacts largely with retention of the configuration both with 3-hydroxypyridine and its 6-methyl homologue. The specific rotation for the latter, $[\alpha]_D = +71°$, is the same as for the reference compound obtained from the corresponding amino acid.[8] The less optically stable desmethyl product had specific rotation $[\alpha]_D = +27°$ while the value for the reference compound in this case was only $+5°$.[9]

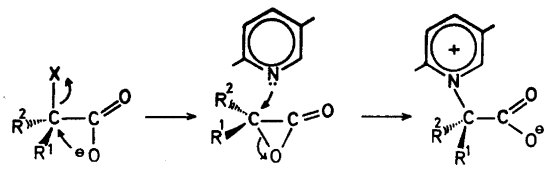
Table 1. Optical rotations for the reactions [a,b] given in Scheme 1.

Comp.	R^1	R^2	R^3	R^4	R	X	Solvent [c]	React. time in min	Configuration		Rotation	
									Reagent	Product	$[\alpha]_D$	$[\alpha]_{578}$
IXa	H	OH	H	H	OH	Br	A	5	L	D	−40	
»	»	»	»	»	»	»	B	180	L	D		− 1
»	»	»	»	»	»	»	D	60	L	D		− 7.6
»	»	»	H	H	OH	I	A	20	L	L		+3
»	»	»	»	»	»	»	B	20	L			0
»	»	»	H	H	OH	OTos	A	30	L	L	+30	
»	»	»	»	»	»	»	B	60	L	L	+27	
»	»	»	»	»	»	»	C	60	L	L	+15	
IXb	CH_3	OH	H	H	OH	OTos	B	15	L	L	+71	
IXc	H	OH	CH_3	CH_3	OH	Br	A	240	L	L	+35	
IXd	»	»	H	C_6H_5	OH	Br	A	90	L	D	+10.8	
IXe	»	»	»	CH_2SCH_3	»	»	A	15	D	[d] L	+ 5.6	
Xa		»	H	H	OC_2H_5	»	B	360	D		0	
»	»	»	»	»	»	»	D	60	D	L	+ 3.2	
»	»	»	»	»	»	OTos	A	60	L	D		− 1
»	»	»	»	»	»	»	B	36h	L		0	
»	»	»	»	»	»	»	D	[e] 20	L	D		−10
Xb	H	H	H	H	OC_2H_5	OTos	D	[e] 20	L	[f] D		−14.1
	H	OH	H	$SCH_2C_6H_5$	OH	Br	B	[g] 10	L			
XI	H	OH	H	H	$N(CH_3)_2$	Br	B	20h	DL			

[a] The reactions were run at 80°, unless otherwise stated.
[b] The specific rotations for the acids are recorded in water and for the esters in ethanol.
[c] Solvents: A = $C_6H_5CH_3$, B = CH_3CN, C = DMF, D = Reagent.
[d] Configuration determined by ORD and CD measurements to be reported on separately.
[e] The temperature used was 70°.
[f] The configuration is not known, but can be assumed to be D by analogy with the reaction with 3-hydroxypyridine.
[g] The temperature used was 20°.

Since the reaction conditions are the same in each case it must be the nature of the leaving group which decides the pathway and stereospecificity of the reaction. The stereochemical inversion in the reaction between pyridines and 2-bromopropionic acid could be expected from analogous reactions between 2-bromocarboxylic acids and ammonia. These reactions go with inversion of the configuration if the C-3 carbon carries no more than one substituent.[20] The retention of the configuration for the 2-tosyloxypropionic acid in the Menschutkin reaction must be explained by a much increased activation energy for the S_N2 transition state so the molecule reacts according to an S_Ni mechanism due to the bulkiness of the tosyloxy group and also in part to the size of the pyridyl nucleophile. The bulkiness of the pyridyl nucleophile is not decisive, however, since aminolysis of L-(−)-tosyloxypropionic acid was also found to give L-(+)-alanine.

L-(−)-Bromoisovaleric acid also reacts with retention of the configuration. The specific rotation, $[\alpha]_D = +35°$, (reference $+30°$) points to a stereospecific mechanism as found in aminolysis.[14] Thus the substituents causing steric crowding in the molecule can be attached to either the C-2 or C-3 carbon. In such cases an alternative transition state is energetically favoured in which the nucleophilic carboxylate oxygen displaces the leaving group and is itself displaced by the pyridyl nucleophile.



XII XIII XIV

These substitution reactions are kinetically controlled. 2-Bromopropionic acid and 2-bromoisovaleric acid in ammonia will have the carboxyl group in the nucleophilic carboxylate form. Despite this the S_N2 transition state for the propionic acid is energetically so favoured that the amino acid, formed with Walden inversion, is optically very pure. The isovaleric acid and tosyloxypropionic acid gave amino acids with unchanged configuration and with about the same optical purity.

Aminolysis of the corresponding 2-bromo amides goes with inversion of the configuration.[20] Studies of the reaction between 2-tosyloxypropionic acid and LiCl show Walden inversion, but as a carboxylate salt the propionic acid reacts with LiCl with retention of the configuration.[21]

These results are difficult to apply directly to our findings in the Menschutkin reaction. 3-Hydroxypyridine is a weak base and will not much affect the slight dissociation of the acid reagent in toluene. The dissociation will be further decreased by the acidity of the carboxyl group in the condensation product (p*K*a 1.8). Despite the unfavourable conditions for carboxylate formation the reactions with the bromoisovaleric acid and the tosyloxypropionic acid are stereospecific with configurational retention. This means

that the activation energy for the S_N2 transition state involving the pyridyl nucleophile is so high that an S_Ni transition state with the carboxyl oxygen as nucleophile becomes important. An alternative explanation lies in some carboxylate formation from dimeric acid in the acid aggregates in toluene.

In agreement with the configurational assignments the reactions which go with configurational retention show reduced reaction rates. Thus the bromoisovaleric acid and the bromopropionic acid had reacted to about the same extent after 4 h and after 5 min, respectively. With a phenyl substituent on the C-3 carbon (IV) instead of the two methyl groups the reaction time was reduced to 1½ h. The specific rotation, $[\alpha]_D$ +10° as compared to +70° for the reference compound, shows the product to be largely racemised. The relatively low optical stability of the product [19] makes difficult an assessment of the stereospecificity of the reaction.

The sulphur in thioethers is a very good neighbouring group participant in displacement reactions. Such a derivative was therefore prepared from the *S*-benzyl derivative of L-cysteine [11] and reacted with 3-pyridinol. Sulphur participation was clearly demonstrated by the bromo reagent being so active that the reaction had to be carried out in the cold. Chromatography showed that three major products were formed. The initial condensation product is highly active and will undergo further reactions, especially eliminations.

The sulphur was then moved one methylene group away from the α-carbon by using D-methionine as precursor.[12] Sulphur participation now would involve a non-favourable 4-membered ring. In agreement with this the reaction rate was very much the same as in simple propionyl derivatives and the reaction proceeded with net inversion of the configuration, as measured by ORD/CD,[22] but the degree of racemisation appears to be high.

The amide and the esters of 2-substituted propionic acid reacted much more slowly than the corresponding acids with 3-hydroxypyridine although the amide group or the ester group should introduce little additional steric hindrance. The difference in reaction rate is more clearly demonstrated for the larger nucleophile 3-hydroxy-6-methylpyridine. The latter reacts readily with 2-tosyloxypropionic acid with configurational retention in acetonitrile but hardly at all with the ethyl ester where the carboxyl function is blocked.

Both ethyl bromopropionate and ethyl tosyloxypropionate gives optically active products with 3-hydroxypyridine if the esters are used as solvent and the reaction time is short. There is a net inversion of the configuration but the stereospecificity of the reaction is probably considerably higher than it appears to be because of the low optical stability of the ester products. Even so the tosyloxy ester product had specific rotation $[\alpha]_{578} = -10°$. After ester hydrolysis the value was $[\alpha]_{578} = -33°$ which shows high stereospecificity.

EXPERIMENTAL

Besides the use of spectroscopy the reactions were followed by paper chromatography and TLC on silica gel in BuOH:EtOH:NH_3:H_2O (4:1:2:1:) and BuOH:HOAc:H_2O (100:22:50).

UV and NMR data have previously been reported.[8,7]

2-(3-Hydroxypyridinium)propionate [9] *(IXa):* (a) A solution of the α-substituted propionic acid (0.01 mol) and 3-hydroxypyridine (0.01 mol) in toluene (25 ml) was

heated to 80° for various lengths of time (Table 1). The product formed appeared in a separate phase. The solvent was then decanted, the residue dissolved in ethanol and precipitated by ether addition. The semisolid was redissolved in ethanol and a little ether added. The title compound crystallized out slowly from this solution; m.p. 162° (decomp.).

(b) The reactants in the above mol ratio were heated at 80° in DMF for 1 h. The solvent was distilled off at reduced pressure and the residue crystallized from ethanol-ether.

(c) The reactants in the above mol ratio were heated together in acetonitrile at 80° for various lengths of time (Table 1) and the reaction mixture worked up as under (b).

(d) L-Bromopropionic acid (0.02 mol) and 3-hydroxypyridine (0.01 mol) were heated together with stirring at 80° for 1 h. The excess bromopropionic acid was distilled off at reduced pressure and the residue worked up as under (b).

2-(3-Hydroxy-6-methylpyridinium)propionate[8] *(IXb).* The title compound was prepared from 3-hydroxy-6-methyl-pyridine and isolated as above under (b).

2-(3-Hydroxypyridinium)-3-phenylpropionate (IX d), m.p. 152° (decomp.) and *2-(3-hydroxypyridinium)-3,3-dimethylpropionate*[9] *(IX c),* m.p. 148° (decomp.) were both prepared from the corresponding α-bromo acids as above under (a). The zwitterions were here isolated from their hydrobromide salts by passage of an aqueous solution through DEAE-25 Sephadex column in the amine form. The zwitterions were eluted with 0.5 N formic acid.

2-(3-Hydroxypyridinium)-4-methylthiobutyrate (IX e), was prepared from the corresponding α-bromo acid as above under (a), m.p. 155° (decomp.). (Found: C 52.61; H 5.77; N 6.15. Calc. for $C_{10}H_{13}NO_3S$: C 52.90; H 5.68; N 5.89.)

Ethyl 2-(3-hydroxypyridinium)propionate p-*toluenesulphonate (X a).* (a) Ethyl D-(−)-tosyloxypropionate, $[\alpha]_{578}^{20} = -47.5°$, (1.09 g, 0.004 mol) and 3-hydroxypyridine (0.38 g, 0.004 mol) were heated together at 70° with stirring for 20 min. The reaction mixture was then dissolved in ethanol (20 ml). The title compound crystallized out on slow addition of ether and was recrystallized from ethanol; yield 0.54 g (37 %), $[\alpha]_{578}^{20} = -7.0°$ ($c = 10$ in ethanol). With two equivalents of the tosyloxy ester the yield was increased to 43 % and the specific rotation to −8.6°.

Four equivalents of the ester gave specific rotation −10.0° without increase in the yield; white crystalline material, m.p. 141 − 142°.

(b) 0.01 mol of the above reangents were heated together in toluene (25 ml) at 80° for 1 h. The solid precipitate was recrystallized from ethanol-ether; yield 10 %, m.p. 151 − 152°, $[\alpha]_{578}^{20} = -1.0°$ ($c = 5$ in methanol).

(c) 0.02 mol of the above reagents in acetonitrile (200 ml) after 3½ days at 80° gave 60 % of the fully racemised product, m.p. 155 − 156°. (Found: C 56.07; H 6.13; N 4.11. Calc. for $C_{17}H_{21}NO_6S$: C 55.60; H 5.73; N 3.81.)

Ethyl 2-pyridiniumpropionate p-*toluenesulphonate (Xb),* was prepared as above under (a) by heating pyridine and ethyl 2-tosyloxypropionate at 70° for 20 min. The product had m.p. 126 − 127°. (Found: C 57.84; H 5.94; N 3.90. Calc. for $C_{17}H_{21}NO_5S$: C 58.11; H 6.02; N 3.99.)

Ethyl 2-(3-hydroxypyridinium)propionate bromide (Xa), was prepared from ethyl D-bromopropionate as under (a) and (c).

2-(3-Hydroxypyridinium)N,N-dimethylpropionamide bromide (XI). 2-Bromo-*N,N*-dimethylpropionamide (5.40 g, 0.03 mol) and 3-hydroxypyridine (2.85 g, 0.03 mol) were heated together in acetonitrile (150 ml) for 20 h at 80°. The solution was then concentrated to one third of its volume and ether (10 ml) added to precipitate the title compound; yield 5.0 g (60 − 70 %). Further recrystallisations from ethanol-ether gave m.p. 214 − 216°. (Found: C 44.32; H 5.31; N 10.31. Calc. for $C_{10}H_{14}N_2 \cdot HBr$: C 43.70; H 5.46; N 10.0.)

Hydrolysis of ethyl esters (Xa). The esters could be hydrolysed simply by heating the ester bromide or tosylate in boiling water for 10 − 15 h. The hydrolysis is much faster on addition of hydrochloric acid. The zwitterion was obtained by passing aqueous solutions of the zwitterion through DEAE-25 Sephadex column followed by elution with 0.2 N formic acid.

Racemisation of 2-bromopropionic acid. To a solution of L-2-bromopropionic acid (0.59 g) in acetonitrile (5 ml) was added 2 drops of conc. HBr. The specific rotation was then $[\alpha]_D^{25} = -3.86°$. After heating at 80° for 1 h the rotation was reduced to −0.90° *i.e.*, a 77 % reduction. An experiment without HBr addition showed no change in the rotation.

Racemisation of D-*2-(3-hydroxypyridinium)propionate* p-*toluenesulphonate (IXa).* 0.253 g of the ester dissolved in acetonitrile (5 ml) had $[\alpha]_D^{25} = -0.53°$. The rotation did not change to any extent on addition of a little 3-hydroxypyridine. When the solution was heated at 80° for 1 h, however, the rotation was −0.29° corresponding to 45 % reduction in activity. A blank without 3-hydroxypyridine showed no racemisation.

A similar experiment with pyridine addition lowered the rotation by 30 %.

L-*(+)-Alanine hydrochloride.* A solution of L-tosyloxypropionic acid (2.44 g, 0.01 mol) in absolute ethanol (40 ml) was saturated with ammonia at 0°. After 3 days at 20° the solution was evaporated to dryness, the residue dissolved in 6 N HCl and the solution extracted with ether. The aqueous solution was then evaporated to dryness and the residue triturated with acetone. The solid residue, which is the title compound slightly contaminated by ammonium chloride, had specific rotation $[\alpha]_{546}^{20} + 4°$ ($c = 2$ in H_2O).

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