THE WALDEN INVERSION—A CRITICAL REVIEW.

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In 1891, Walden asserted that by means of a simple cycle, he could pass directly from one optically active acid to its antipode. By treatment of natural l malic acid, for example, with phosphorus pentachloride, he obtained a laevorotatory chlorosuccinic acid, in which, by subsequent treatment with moist silver oxide, he was able to substitute hydroxyl (OH) for chlorine (Cl), and recover the hydroxy acid used as starting material. To his great surprise, however, the malic acid thus obtained was strongly dextrorotatory. When Walden used, in place of moist silver oxide, stronger bases, e.g. potassium or sodium hydroxide, he recovered the original l malic acid. An inversion in optical activity must have occurred, therefore, in his first cycle either with phosphorus pentachloride or with silver oxide.

This work was ridiculed by all of the leading chemists at that time, since it was entirely out of harmony with the ideas advanced by Vant Hoff and Le Bel. These men had pointed out that all of the optically active bodies studied by Pasteur had at least one asymmetric carbon atom (meaning by ‘asymmetric,’ that all of the atoms or groups attached to such a C atom were different each from the other). This idea had served to put the chemistry of the optically active bodies on a substantial and rational basis. Earlier chemists had been forced to assign different structural formulae to optical isomers—for a long time the formula $\text{CH}_2\text{OH}-\text{CH}_2-\text{COOH}$ was given to ‘fleischmilch-

1 Ber, 28, 1293.
2 Wissenschaft: Ann. 166, 6; Moldenhauer: Ann. 131, 323.
säure’ (d lactic acid) to distinguish it from ‘gährungs milchsäure’ (dl lactic). According to Vant ’Hoff’s idea, the difference in physical properties of optical antipodes could be indicated structurally in a simple manner by means of a different arrangement of the various groups around the asymmetric carbon atom.

To maintain a rational system it was necessary, of course, that in the simple exchange of one radical for another in an optically active compound by means of various reagents, no rearrangement of the atoms in space should occur—in other words, the substituted product should have a structure corresponding to that of the original material, as is represented by the following scheme:

\[
\begin{align*}
\text{COOH} &\quad \text{COOH} &\quad \text{COOH} \\
\text{HO-\(\cdot\)-C-H} + \text{PCl}_3 &\rightarrow \text{Cl-C-H} &\quad \text{H-O-\(\cdot\)-C-H} + \text{KOH} &\rightarrow \text{H-C-H} \\
\text{HC-H} &\quad \text{HCH} &\quad \text{COOH} &\quad \text{COOH} \\
1\text{ malic} &\quad 1\text{ chlorosuccinic} &\quad 1\text{ malic} &\quad 1\text{ malic}
\end{align*}
\]

Walden determined that these changes took place as indicated, both of which according to his latest work he regarded as normal. He discovered, however, that by using moist silver oxide to replace the halogen, he always obtained an abnormal result (a product which demanded a rearrangement of the atoms in space). Such an abnormal result always lights the way to a new discovery, and demands an extension or revision of our present theory. Walden was, therefore, not slow in announcing that he had obtained an inversion in the optical activity of malic acid by means of a simple cycle in which OH was replaced by Cl using phosphorus pentachloride, and the halogen atom, in turn, was replaced by hydroxyl using moist silver oxide—whence the name, the ‘Walden inversion.’

\[
\begin{align*}
\text{COOH} &\quad \text{COOH} &\quad \text{COOH} \\
\text{HO-\(\cdot\)-C-H} + \text{PCl}_3 &\rightarrow \text{Cl-C-H} &\quad \text{H-O-\(\cdot\)-C-H} + \text{AgCl} &\rightarrow \text{H-C-OH} \\
\text{HC-H} &\quad \text{HCH} &\quad \text{COOH} &\quad \text{COOH} \\
1\text{ malic} &\quad 1\text{ chlorosuccinic} &\quad d\text{ malic}
\end{align*}
\]
That such an inversion actually takes place is wonderful indeed and, in my opinion, still remains to be proved, in spite of the apparently absolute demonstration by Walden, Purdie, Fisher, McKenzie and many others. Some recent experimental work which I have done, indicates that the acid product obtained by the action of silver oxide in water solution on dl bromopropionic acid (a change entirely analogous to the one given above) has properties entirely different from those of ordinary dl lactic acid. This evidence will be discussed at greater length in the experimental part of this paper. Since some confirmatory evidence in the absolute proof to the contrary is still lacking, let us assume here for simplicity, that the Walden inversion is an established fact.

For a long time Walden was misled by the fact that his chloro-succinic acids gave an actual rotation opposite to that indicated by their sign i.e. d chlorosuccinic rotated laev and vice versa. But he decided finally that the action of phosphorus pentachloride on malic acid was normal, a conclusion which he deduced largely from theoretical and physico-chemical considerations. Having determined this, it followed as a matter of course that the action of potassium hydroxide was normal, while that of moist silver oxide was abnormal. The question as to whether the action of nitrous acid on asparaginic acid to give malic was normal or abnormal, Walden left open, since he was unable to determine. Having contributed a splendid and practically complete demonstration of the chemistry of the optically active malic acid series, Walden published the last of his five papers in 1899, and left this field of work.

With the exception of a small but very significant contribution by Purdie and Williamson,5 nothing of vital importance was done on the Walden inversion from 1899 until March, 1907, when Emil Fisher published his first article, "Zur Kenntnis der Waldensche Umkehrung." In synthesizing various optically active polypeptides, Fisher was forced to determine absolutely

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5 Berichte 22, 1855.
4 Ber., 32, 1833 and 1855.
6 Ber., 40, 1051.
by experiment whether there was anything in the idea of the Walden inversion i.e. whether by use of certain reagents, he might obtain, not the corresponding substituted product, but its optical antipode. This could only be determined by careful experiment, since the sign of actual rotation whether dextro or laevo, is no positive indication as to whether the body is really a (d) or an (l) derivative. Fisher not only confirmed the work of Walden by showing that an analogous inversion takes place with a bromopropionic acid by the successive action of phosphorus pentachloride and moist silver carbonate, but he also discovered another case where the change was accompanied by inversion, namely the conversion of optically active alanin into bromopropionic acid, using nitrosyl bromide (NOBr) as the brominating agent.

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\begin{align*}
\text{COOH} + \text{NOBr} & \rightarrow \text{BrC} - \text{H} + \text{N}_2 + \text{H}_2\text{O} \\
\text{CH}_3 - \text{H} + \text{N}_2 + \text{H}_2\text{O} & \\
\text{d alanin} & \rightarrow 1 \text{ bromopropionic}
\end{align*}
\]

Fisher rigidly established that the Walden inversion was confined to these two phases: Phase 1—replacement of Cl by OH by means of silver oxide or other bases of the same type. Phase 2—replacement of amino (NH$_2$) group by halogen, using nitrosyl halide as agent. That the action of phosphorus pentachloride was normal, while that of nitrosyl bromide was abnormal, he established as follows:

- d lactic acid + PBr$_3$ → d bromopropionic acid (dextrorotatory)
- d lactic ethyl ester + PBr$_3$ → d bromopropionic ethyl ester (dextrorotatory)
- d alanin + NOBr → 1 bromopropionic acid (laevo-rotatory)
- d alanin ethyl ester + NOBr → d bromopropionic ethyl ester (dextro-rotatory).

Other evidence of course was furnished, but the main point in Fisher’s proof was the comparison of results obtained by various reagents on the free acids and their corresponding esters. If these two actions were analogous, the substituting agent reacted normally; if different products were obtained in the two actions, an inversion must have occurred in the case of
the free acid. That the inversion took place with the free acid rather than with the ester, Fisher decided from the fact that esters were less inclined to optical reversals than the corresponding acids. Having established as above that the action of phosphorus pentachloride or pentabromide resp. was normal, it followed that the subsequent action of potassium hydroxide on the brom acid, thus formed from lactic, was normal, while that of moist silver carbonate on the same brom acid was abnormal just as Walden finally decided. The correctness of the above reasoning Fisher also established as follows by direct experiment.

\[
\begin{align*}
\text{d brompropionic acid + KOH} & \rightarrow \text{d lactic acid (–Zn salt)} \\
\text{d brompropionic acid + Ag}_2\text{O} & \rightarrow \text{1 lactic acid (+Zn salt)} \\
\text{d brompropionyl glyc\text{in + Ag}_2\text{O}} & \rightarrow \text{d lactic ester (Free acid obt. by hydrolysis gave negative zinc salt).}
\end{align*}
\]

The actions of ammonia and of nitrous acid (nitrous fumes) were held to be normal from a consideration of the following reactions:

\[
\begin{align*}
\text{d brompropionic acid + NH}_3 & \rightarrow \text{d alanin (dextrorotatory)} \\
\text{d brompropionic ethyl ester + NH}_3 & \rightarrow \text{d alanin ethyl ester (dextrorotatory)} \\
\text{d alanin + N}_2\text{O}_3 & \rightarrow \text{d lactic acid (Negative zinc salt)} \\
\text{d alanin ethyl ester + N}_2\text{O}_3 & \rightarrow \text{d lactic ethyl ester (Free acid obt. by hydrolysis gave negative zinc salt).}
\end{align*}
\]

Walden had tried the action of ammonia on chlorsuccinic acid but failed to get asparaginic acid. Fisher, by repeating Walden’s experiment later, was able to isolate a small amount of the amino acid in this way. This fact is quite significant since it serves to bring out another important point. The formation of monoamino acid, by the action of concentrated aqueous ammonia on the halogen substituted acids, never takes place alone as most writers seem to imply. We sometimes have di and triamino acids formed in this action (vide Heintz) and since ammonia acts also as a weak base, as well as an amino compound, we ought to have a large or small amount of hydroxy-

\footnotesize{7 Fisher and Raske: Ber. 46, 1051–7.  
\footnotesize{8 Heintz: Ann. 156, 25; Ann. 136, 213–223.}
acid always formed simultaneously. These facts may have an important bearing when we test experimentally the second phase of the Walden inversion brought out by Fisher, namely the apparent inversion in the action of nitrosyl bromid on the amino acid and the normal reaction obtained with ammonia on the brom acid to give the corresponding amino acid. In this connection, I may add, however, that the action of nitrosyl bromide on alanin gives a quantitative yield of perfectly homogeneous, constant boiling, brom-propionic acid. If the inversion which seems to occur with nitrosyl bromide, does not take place as a matter of fact, we would simply have to shift the names of our aminopropionic acids, i.e. call laevorotatory alanin d alanin and vice versa, and likewise other homologous amino acids. This would involve no very radical change as we now have just such a condition in the case of the halogen succinic acids—we should have the amino group now and then exerting the same general effect on the absolute rotation of the acid or ester as the substituting halogen group sometimes does. If such is the case, we can test the point most readily experimentally by a reinvestigation of the action of nitrous fumes on dl alanin to determine whether dl lactic acid is really obtained or is the only product formed. It is quite reasonable to believe that nitrous acid may give in this case also a body having all the properties of the acid product which we obtained in the action of moist silver oxide or dl brompropionic acid.

Fisher also stated that the inversion seemed to occur only with a substituted acids i.e. at the asymmetric carbon atom next to the free COOH group and that it took place only with the free acid and never with the ester. By substituting C₂H₅ for H in the COOH group, my own experiments as well as those of others have shown that the reactivity of brompropionic acid toward oxide of silver in absolute ether solution at ordinary temperature is reduced from an extremely high value to practically zero. By thus reducing the speed of the reaction we should naturally expect to get a normal result in the replacement of halogen by hydroxyl using oxide of silver as substituting

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* Same as No. 8.
agent. That an inversion should not take place with esters much more reactive than brompropionic, is not at all inconceivable if it really does take place with the free acid; this, however, would supply a serious objection to Fisher's proof of which reagent causes inversion. Later on, \textsuperscript{10} Fisher demonstrated that a $\beta$ halogen substituted fatty acid did not give an inversion with silver oxide and that the action of nitrosyl bromide on the corresponding amino acid was undoubtedly normal in this case also. By moving the halogen one C atom back from the COOH group, the compound ordinarily becomes far less reactive. As a simple illustration of this, we may compare the action of a chlor and $\beta$ chlorpropionic acid with silver oxide.\textsuperscript{11} By checking the speed of the action, we should expect to get a normal replacement of halogen by hydroxyl, using silver oxide as agent, just as Fisher has determined experimentally with $\beta$ chlorbutyric acid. McKenzie very recently\textsuperscript{12} confirms this observation by proving that phenyl $\beta$ brompropionic acid does not give an inversion with silver oxide. There is no reason, however, a priori, for not getting an inversion with very reactive $\beta$ halogen or amino substituted acids as well as $\alpha$.

The phenomena, giving rise to the 'Walden inversion' (real or apparent), take place, as far as I have been able to judge, as the result of a very rapid action. The replacement of halogen by hydroxyl in a perfectly normal manner takes place when the reaction proceeds more slowly.

We must bear in mind the fact that a brompropionic acid forms sodium and potassium salts which have a fair degree of stability towards water and dilute alkali. I have succeeded in recovering sodium brompropionate almost quantitatively from a water solution of the free acid neutralized with sodium hydroxide and subsequently distilled off at reduced pressure (20 mm) heating finally to 60°C; while, contrary to the statement of Beckurts and Otto,\textsuperscript{13} by no conceivable method could I get a trace of

\textsuperscript{10} Ber. (May, 1909), 1219.
\textsuperscript{11} Wischelhaus; Ann. 148, 1. Moldenhauer, Ann. 131, 323.
\textsuperscript{12} J. L. Ch. Soc. March, 1910, p. 121.
the silver salt of a bromoproionic acid by neutralizing with silver oxide. The reaction between silver oxide and bromoproionic acid proceeds with tremendous speed once the short period of induction is passed—hydrogen bromide is split off readily and silver bromide separates out quantitatively in a very short time. According to Senter, a bromoproionic acid, treated in water solution with silver nitrate, gives a reaction 17000 times faster than that of sodium hydroxide on the same acid. With silver oxide in place of silver nitrate, there is also undoubtedly a vast difference in speed between the two reactions. That we are dealing here with two totally different reactions is the opinion of Senter, Burke and Donnan, Euler and others, who have attacked this problem from the physico-chemical standpoint. That different reaction products are formed remains to be rigidly established.

Fisher and Scheibler's Results and McKenzie's Contribution.

We are now in a position to consider some results, which, when viewed in the right light, may turn out to be a reductio ad absurdum disproof of the whole Walden inversion. In the first place we may ask: Can Fisher's explanation of the Walden inversion be followed out to give a completely harmonious system? No. He has found that in the case of d valin (d a aminoisovalerianic acid) a double inversion occurs i. e. an inversion both with nitrosyl bromide and ammonia, so that as a result of this cycle the original valin is regenerated. In this case we may still believe, as Fisher first thought, that no inversion occurs with either reagent, since Fisher and Scheibler found that bromoisovalerianic acid, treated either with potassium hydroxide or with silver oxide, yielded the same hydroxy-acid. Here again we may have, of course, an inversion with both bases—indeed, unless we make such an assumption, the action of nitrous acid must also be considered abnormal, since 1 valin with nitrous acid gives the same oxy-acid as is obtained by the

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16 Ber. 39, 2726–2734.
17 Ber. 41, 889.
18 Ber. 41, 2891.
action of potassium hydroxide or silver oxide on d bromisovalerianic acid. These results, when carefully considered, seem to indicate that there is no inversion of optical activity in any of reactions of optically active valin or its corresponding derivatives. Fisher himself is at a loss in considering these reactions for they show that, if there is anything in the idea of a Walden inversion, the influence of any reagent, whether normal or abnormal, can not be predicted, but must be worked out carefully in each individual case. This necessarily means much tedious work in establishing the changes taking place with optically active substances—as an immediate result it tends to throw some doubt on the absolute configuration of the C₂ acids as established by Fisher on the basis of several changes, all of which were assumed to be normal.

Fisher and Jacobs\(^{19}\) had shown that d serine had a constitution corresponding to that of d glycine, the structure of which had been proved to be similar to that of d tartaric and therefore to d glucose by Neuberg and Silbermann.\(^{20}\)

\[
\begin{array}{c}
\text{COOH} \\
| \text{H} \text{C} \text{NH}_2 \\
| \text{CH}_2 \text{OH}
\end{array} 
\quad \begin{array}{c}
\text{COOH} \\
| \text{H} \text{C} \text{NH}_2 \\
| \text{CH}_2 \text{OH}
\end{array} 
\quad \begin{array}{c}
\text{COOH} \\
| \text{H} \text{C} \text{NH}_2 \\
| \text{CH}_2 \text{OH}
\end{array}
\]

\begin{array}{c}
\text{HC} \text{OH} \\
| \text{CH}_2 \text{OH}
\end{array}
\quad \text{d glycine}
\quad \text{d alanine}

\begin{array}{c}
\text{HC} \text{OH} \\
| \text{CH}_2 \text{OH}
\end{array}
\quad \text{l serine}
\quad \text{d lactic}

\begin{array}{c}
\text{HC} \text{OH} \\
| \text{CH}_2 \text{OH}
\end{array}
\quad \text{l serine}

\begin{array}{c}
\text{HC} \text{OH} \\
| \text{CH}_2 \text{OH}
\end{array}
\quad \text{d glycine}

\]

l serine gives by treatment with nitrous acid the corresponding hydroxy-acid, (l glycerine acid according to Neuberg and Silbermann) or d glycine acid according to Neuberg's latest work (where he shows that d glycine acid by addition of prussic acid etc. gives d tartaric acid).\(^{21}\) d glycine acid has the structural formula therefore as given above

\(^{19}\) Ber. 40, 1057.
\(^{20}\) Zeit. für physiol. Ch. 44, 134 [1906].
\(^{21}\) Bioch. Zeit. 5, 461.
which is in beautiful harmony with the system proposed by Rosanoff. Fisher and Raske succeeded in converting L serine into d alanine,\textsuperscript{23} which in turn by treatment with nitrous acid gave d lactic acid.\textsuperscript{24} We have, therefore, a rigid demonstration of the configuration of the whole series of the C\textsubscript{3} optically active acids, providing of course, that all the exchanges used in this proof take place normally.

Fisher seems to be about to attack this problem from an entirely different point of view. Making use of Guye and Crum Brown's hypothesis i.e. by simply determining the effect of various substituting groups on the absolute rotation of a large number of organic compounds and taking account also of the relative position of the various groups, one may ultimately be able to calculate the rotation produced by a body of a given configuration. Providing no other side products were formed, we would have complete information regarding the changes taking place with optically active bodies as soon as we had determined the rotation of the product. The exact trend of Fisher's future work on the Walden inversion is hard to determine—his last paper on propyl, isopropyl cyanacetic acid\textsuperscript{25} seems to be in the direction indicated here. To attain results of general significance along this line will involve, however, a very considerable amount of tedious work, since the elimination of the effect of the solvent upon the absolute rotation of various substances is a matter of extreme difficulty. Unfortunately, all of our pure organic bodies can not be studied in the form of oils.

We shall now consider some results in another series which may be interpreted on the basis of a double inversion. Shortly after Fisher's first paper was published in March 1907, McKenzie, an English chemist, announced some experimental re-

\textsuperscript{23} Ber. 40, 3717; Ber. 41, 893.
\textsuperscript{24} Ber. 40, 1061.
\textsuperscript{25} Ber. [Sept. 1906] 42, 2981–2989.
results,\textsuperscript{28} obtained with optically active phenyl chloracetic acid, which were entirely out of harmony with Fisher's results obtained in the lactic acid series, as well as those of Walden in the malic acid series. McKenzie quickly seized upon Fisher's double inversion idea as a means of explaining some of his apparently anomalous results (i.e. anomalous in the sense of not harmonizing with Fisher's conception of the Walden inversion as proposed in 1907). He found that optically active mandelic acid, treated with phosphorous pentachloride and then with potassium hydroxide, yielded its antipode while successive treatment with phosphorous pentachloride and oxide of silver gave back the same optically active mandelic acid as was used at the start. To obtain a harmonious explanation of these results, McKenzie, in his second article,\textsuperscript{27} held that the action of phosphorous pentachloride might be considered as abnormal in this case; the action of potassium hydroxide would then be normal and that of silver oxide abnormal just as Fisher and Walden found in other series. But this assumption (that phosphorus pentachloride may act abnormally) did not harmonize with the following observations by the same author.

\[ \text{d mandelic} + \text{POCl}_3 \rightarrow \text{levo rotatory d phenyl chloracetic} \]
\[ \text{ethyl d mandelate} + \text{POCl}_3 \rightarrow \text{levo rotatory d phenyl chloracetic ethyl ester}. \]

He was forced to interpret, therefore, that silver carbonate acted \textit{normally}, just as it may in Fisher's experiment with optically active valin, and that the action of potassium hydroxide was \textit{abnormal}. These results are exactly the opposite of those obtained by Fisher and Walden in the lactic and malic acid series respectively. McKenzie found also that the action of water was \textit{abnormal} comparable to the action of strong bases on halogen acids of this series while Walden found that the action of water was similar to that of silver oxide and other weak bases. When phenylamino acetic acid was treated with nitrosyl bromide and the resulting brom acid treated with ammonia, the original amino acid was recovered. McKenzie explained this

\begin{itemize}
\item \textsuperscript{28} J. L. Ch. Soc. [May 1908] Vol. 33, p. 81.
\item \textsuperscript{27} J. L. Ch. Soc., May 1909, p. 777.
\end{itemize}
result on the basis of an inversion with both reagents entirely analogous to the double inversion which Fisher seems to have rigidly established in the case of optically active valin. There is very little danger that McKenzie will contribute anything startling to our present knowledge of the Walden inversion as he is unquestionably simply following Fisher's lead in another series. As a serious objection to McKenzie's work he has yet to prove, as far as I can see, that his phenyl chloracetic acid, when treated and allowed to stand with solutions of various dilute alkalies in cold water, even by boiling finally for a short time (30 to 60 minutes) actually splits to any considerable extent, or, if it does split completely, that he obtains quantitatively mandelic acid. If very little splitting actually takes place, then McKenzie's results for stronger alkalies in water solution are valueless while oxide of silver, at all events, may be very reasonably held to give a normal substitution product—a result at variance with the facts established by Fisher, Walden and others who have used this reagent. Inasmuch as mandelic acid is a beautiful crystalline body, these crucial experiments, when carefully repeated, ought to give much more definite results than are obtained with malic and lactic acid since both of the latter give oily derivatives difficult to identify sharply. Of course it must be admitted that the introduction of the phenyl group exerts a powerful influence, but it may be said in this connection that monochloracetic acid gives sodium and potassium salts which are very stable in water and alkaline solution while the halogen, being in the α position, is very easily removed with silver oxide.

As I have tried to point out, future progress in disentangling the 'Walden inversion' will depend not on establishing more analogous inversions in other series, for this will simply add to the confusion already existing.

A rational explanation for the results obtained, where an inversion of optical activity appears to take place, will undoubt-

edly be found as a result of most careful experiments to establish the changes which actually occur in the action of various reagents on optically active bodies, all of which have been assumed to take place as a result of a simple metalization. Scarcely any of these changes have been rigidly established. Almost without exception, satisfactory figures for solubility, water of hydration and percentage of zinc have sufficed to prove the presence of lactic acid in the form of its zinc salt. When the reader weighs carefully the evidence presented in the experimental part of this paper, he will undoubtedly agree with me that the Walden inversion simply represents another case of some peculiar co-incident results which have often led scientists astray.

Some recent experimental results.

This investigation was undertaken at the suggestion of Prof. J. U. Nef of the University of Chicago with the purpose of obtaining independent experimental evidence to support his idea that the four valences of the carbon atom are not mutually equivalent, but only in pairs. According to this idea we ought to be able to prepare two space isomeric diazo propionic esters resp. d and l.

\[
\begin{align*}
\text{d body} & \quad \text{N}^+ \quad \text{CH}_2 \quad \text{C} \quad \text{COOR} \\
\text{l body} & \quad \text{N}^- \quad \text{CH}_2 \quad \text{C} \quad \text{COOR}
\end{align*}
\]

The preparation of diazo fatty esters is no easy matter and besides it was necessary first to become thoroughly familiar with the properties of the optically active acids of the C\textsubscript{3} series.

Optically active alanin was prepared according to Fisher's method by resolution of benzoil alanin by means of brucin in

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aqueous solution. The laevorotatory alanin, thus obtained, was converted by means of nitrosyl bromide quantitatively into dextrorotatory d brompropionic acid according to the latest method of Fisher and Raske. The active brom acid, as prepared, contained 4.38% of optical antipode as against 3% usually found by Fisher.

Inasmuch as nearly all of the experiments, where an inversion was observed, had been carried out in water solution, we attempted to ascertain whether the same inversion occurred in non-aqueous solution in order to establish, first of all, the influence of the solvent. To avoid also the presence of any possible trace of free base, Prof. Nef proposed the idea of studying the action of silver acetate (1 mol) on d brompropionic acid in absolute ether solution.

By hydrolysis of the crude (acylated?) gum thus obtained, and subsequent heating in water solution with zinc carbonate, a difficulty soluble crystalline zinc salt was obtained having all the properties of zinc lactate. Most of this material was inactive—silver acetate seems to have, therefore, a pronounced racemizing effect just as Marekwald and Nolda have found in its action on optically active amyl haloids at higher temperatures. The mother liquor contained a considerable amount of zinc salt which was strongly dextrorotary, from this fact we may assume, as others have done, that there is formed here a little l lactic acid, mixed with a large amount of dl lactic i.e. an inversion has occurred with silver acetate in absolute ether as well as with silver salts in water solution. The solvent undoubtedly causes a difference in the amount of racemation but does not alter the character of the action as far as inversion is concerned.

By the action of silver acetate (1 mol.) in water solution, potassium acetate (1 mol.) in absolute alcohol solution, and sodium hydroxide (1 mol.) in 0.1% water solution on d brompropionic acid there was obtained after hydrolysis in every case, on treatment with zinc carbonate, a difficulty soluble crystalline zinc salt which was more strongly dextrorotatory than that obtained in the experiment with silver acetate in absolute ether.
In accordance with the usual interpretation that nothing but lactic acid is obtained here as ultimate product, we have here in each of these three cases an inversion of optical activity. These experiments serve to disprove Walden's idea that the inversion takes place only with silver hydroxide, water, and analogous weak bases and never with bases or salts derived from such metals as sodium, potassium, etc., whose action on water gives rise to the strong bases. As a result, we see that the inversion may occur in any solvent, aqueous or non-aqueous, and is caused by comparable very slight concentrations of all bases, and of those salts which give bases by dissociation or hydrolysis. That an inversion of optical activity really takes place in any case, in the action of weak bases on halogen substituted fatty acids, becomes decidedly open to question when we consider the following data obtained from experiments with dl (inactive) brompropionic acid.

Space will not permit me to give, as I should like, a detailed description of all the experiments which I have carried out in order to determine the changes taking place in the action of silver oxide and silver salts on d and dl brompropionic acid. I shall content myself with the following summary of results with dl mat.

In the action of silver acetate on d, l or dl brompropionic acid in absolute ether we should expect to get by double decomposition, complete transformation to a acetyl hydroxy-propionic acid (acetylated lactic) soluble in water of b. pt. 134° (15 mm.).

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{HOBr} + \text{AgOOCH}_3 & \rightarrow \text{HO} - \text{O} - \text{C} - \text{CH}_3 + \text{Ag Br}
\end{align*}
\]

\[
\begin{align*}
\text{COOH} & \quad \text{COOH} \\
1\text{ brompropionic} & \quad 1\text{ acetyl hydroxy propionic acid.}
\end{align*}
\]

We get, however, as main product a stiff gum insoluble in water. This gum by hydrolysis with water should give lactic acid of it consisted of oily lactid or poly lactyl lactic acid. By hydrolysis and distillation of the water at reduced pressure, I obtained, to my surprise, in place of mobile, syrupy lactic acid titrating over 90% in the cold, a gum, soluble in water, which had but very little mobility and which, with N/10 potassium hydroxide, titrated only 50% as a free acid. This
hydrolyzed product therefore had all the properties of the acid gum obtained by hydrolysis of the crude product of the action of silver acetate on d brompropionic acid in absolute ether.

Silver oxide, as well as silver carbonate, in water solution yielded a gum which was soluble in water and titrated for the most part as a free acid. By heating, however, with water at 120° for 6 hrs. in oil bath, there was obtained, after distilling off water at reduced pressure, a stiff gum which was soluble in water and titrated only 50% as a free acid. Even after dissolving in excess of 5% soda solution, and heating alkaline solution 5-6 hrs. at 100° the gum recovered by neutralization with stand. dil. HCl, distilling off water at reduced pressure etc., was soluble in water but had very little mobility and titrated only 50-60% as a free acid. Can heating in water solution at 100° in the presence of an excess of zinc carbonate convert this material into zinc lactate, where heating with water at 120°, or with an excess of sodium carbonate at 100° did not yield lactic acid or sodium lactate resp.?

Acrylic acid or hydrracrylic acid might easily be obtained here.

\[
\text{CH}_2\text{C} = \text{COOH} + \text{AgOH} \rightarrow \text{CH}_2\text{H} = \text{CH} \cdot \text{COOH} + \text{AgBr}
\]

If the acrylic acid then in part added water again we should get hydrracrylic acid (β hydroxy propionic).

\[
\text{CH}_2\text{H} = \text{CH} - \text{COOH} + \text{HOH} \rightarrow \text{CH}_2\text{OH} - \text{CH}_2\text{COOH}
\]

That neither of these is present is shown by the fact that the zinc salt crystallizes almost completely from water due to its difficult solubility, while the zinc salts of acrylic and hydrracrylic acids are readily soluble in water.

Dilactic acid might be formed by simple metalepsis:

\[
\begin{align*}
\text{CH}_3 & \quad \text{H} \\
\text{Ag} & \quad \text{Br} \\
\text{O} & \\
\text{Ag} & \quad \text{Br} \\
\text{CH}_2 & \quad \text{C} - \text{COOH}
\end{align*}
\]
That dilactic acid is not present is shown by the fact that the crude acid product obtained by the action of silver oxide on dl bromopropionic, although proved to be homogeneous, shows no tendency to crystallize. In addition brucin dilactate was found to have dec. pt. 110°–138° while the brucin salt of the crude acid gum melts 200°–212° very similar to that of brucin lactate, and other high melting brucin salts.

From the standpoint of dissociation according to Nef, carboxyethyldene is formed first as intermediate product. By subsequent addition of unchanged bromopropionic acid we should expect as the ultimate product not dilactic acid but its structural isomer which exists in two space isomeric modifications:

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{H} & \quad \text{Br} \\
\text{COOH} & \quad \text{COOH}
\end{align*}
\]

\[
2 \text{C} \quad \text{H}_2 \quad \text{Br} \quad \rightarrow \quad \text{HC} \quad \text{C} \quad \text{Br} \quad \text{Br} \quad \text{C} \quad \text{H}
\]

\[
\begin{align*}
\text{COOH} & \quad \text{COOH} \\
\text{COOH} & \quad \text{COOH} \\
\text{COOH} & \quad \text{COOH} \\
\text{COOH} & \quad \text{COOH}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{HC} & \quad \text{C} \quad \text{Br} + \text{AgOH} \quad \rightarrow \quad \text{HC} \quad \text{C} \quad \text{OH} + \text{Ag Br}
\end{align*}
\]

Work is now being continued along this line by the author of this article in the chemical laboratory of Beloit college. An attempt will be made to prepare this body synthetically and study its properties. From its structure we should expect it to behave very similar to lactic or dilactic acid and in addition it ought to give very readily a 1, 2 lactone.

In conclusion, I will say that, by using absolute ether in place of water as solvent, one is enabled to study the action of silver oxide on the simple esters of the halogen substituted fatty acids without danger of hydrolysis. In marked contrast to the behavior of the free acid, dl bromopropionic ester does not react at room temp. with silver oxide in absolute ether solution. By
heating dl brompropionic ethylester with silver oxide several hours at 120° the main product in the action was dilactic diethyl ester just as in the action of the sodium salt of lactic ethyl ester on dl brom propionic ester, according to von Bruggen.

\[
\begin{align*}
\text{H} & \equiv \text{O} \\
\text{CH}_3 - & \text{C} - \text{C} - \text{O} \text{C}_2 \text{H}_5 \\
\text{Br} & \text{Ag} \\
\text{O} \\
\text{CH}_3 - & \text{C} - \text{C} - \text{O} \text{C}_2 \text{H}_5 \\
\text{H} & \equiv \text{O}
\end{align*}
\]

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\[
\begin{align*}
\text{CH}_3\text{C} & \text{CH}_2\text{COOH} \\
\text{Br} & \\
\text{O} & \\
\text{H} & \\
\text{CH}_3\text{C} & \text{C} = \text{C} \text{COOH} + \text{HBr}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{C} & \text{CH}_2\text{COOH} + \text{HOH} \\
\text{Br} & \\
\text{O} & \\
\text{H} & \\
\text{CH}_3\text{C} & \text{C} \text{COOH} + \text{HBr}
\end{align*}
\]


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