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Contributors

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THE CONSTITUTION OF PILOCARPINE

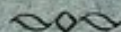
PART V.

CONVERSION OF ISOPILOCARPINE INTO PILOCARPINE

BY

H. A. D. JOWETT, D.Sc.

(From the Transactions of the Chemical Society, 1905)



THE WELLCOME CHEMICAL RESEARCH LABORATORIES

FREDERICK B. POWER, PH.D., *Director*

6, King Street, Snow Hill

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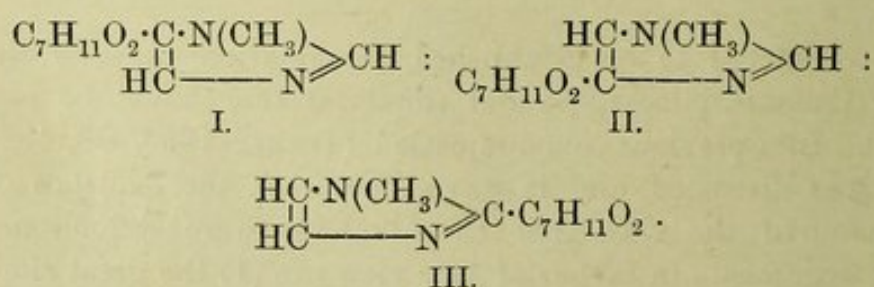
(Continued on page 3 of cover)

and (2) the difference in their behaviour towards chromic acid, pilocarpine yielding pilocarpoic acid, $C_{11}H_{16}O_5N_2$, whilst in the case of isopilocarpine no definite product could be isolated.

With regard to the first argument, it was pointed out that the apparent difference in the action of bromine might be accounted for by assuming that a similar reaction occurred in each case, but that the isomeric products differed in their facility of crystallising; in each case the yield of crystalline acid is small, thus proving that the substance isolated does not represent the whole product of the reaction, and furthermore the alkaloids are known to yield isomeric substances differing in their ability to crystallise, for example, pilocarpine methiodide is amorphous, whilst isopilocarpine methiodide is crystalline. Thus it is possible that bromocarpinic acid is crystalline, whilst bromoisocarpinic acid is amorphous, and dibromopilocarpinic acid amorphous, whilst the corresponding isomeride is crystalline.

With respect to the second argument, it was shown (*loc. cit.*) that the reaction of pilocarpine with chromic acid had not been sufficiently studied to admit of any deduction being made in favour of either theory. In the meantime, the action of chromic acid on pilocarpine and the properties of the two bromo-acids above mentioned have been further studied by Pinner (*Ber.*, 1905, 38, 1510). He, however, is of opinion that the isomerism is not due solely to stereochemical causes, but that the alkaloids are structural isomerides, and that this isomerism depends on the point of attachment of the pilopic complex, $C_7H_{11}O_2$, to the glyoxaline ring. But as I have previously pointed out, there are several objections to this explanation.

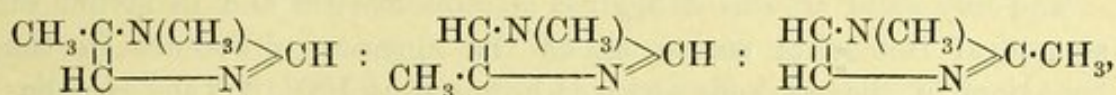
The three possible formulæ are:



If I be accepted as the constitutional formula for isopilocarpine, then pilocarpine must be represented by formula II or III. But II is so similar to I that it would not explain the apparent difference in the behaviour of the alkaloids towards bromine or chromic acid, whilst III is, as Pinner admits, improbable, for it is difficult to conceive how the group $C_7H_{11}O_2$ could pass from the carbon atom to the other as required in formula I.

Furthermore, if such a change took place in the case of the grouping such as $C_7H_{11}O_2$, one would expect it to occur with greater facility

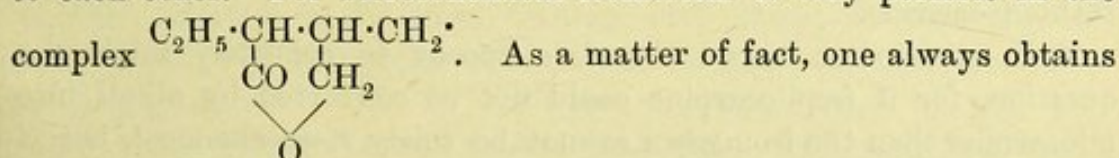
when this complex is replaced by a simpler group such as CH_3 . But the three glyoxalines of the following formulæ are known :



and in the course of their preparation have been distilled at a somewhat high temperature (above 200°). Therefore no such change occurs with these simple glyoxalines, and it is unlikely that a group such as $\text{C}_7\text{H}_{11}\text{O}_2$ would migrate when the simple CH_3 group shows no such tendency.

Pinner's recent work also affords an explanation of the apparent difference in the reaction of the alkaloids with chromic acid. He has shown that pilocarpoic acid can be converted into the isomeric *isopilocarpoic* acid by means exactly analogous to those employed for converting pilocarpine into *isopilocarpine*, and there is little doubt that the same relation exists between the isomeric acids as between the alkaloids. The failure to isolate the *isopilocarpoic* acid from the reaction of *isopilocarpine* with chromic acid would therefore appear to be due solely to experimental difficulties.

Pinner's chief argument against stereoisomerism is open to serious objection. He states, "The conversion of pilocarpine and its derivatives into the *iso*-form cannot be simply a stereochemical rearrangement, but must consist in a change in the arrangement of the atoms to each other. For stereochemical isomerism is only possible in the



isomeric compounds from pilocarpine and *isopilocarpine* so long as the glyoxaline ring remains intact. As soon as compounds are formed in which this group no longer exists, it is immaterial whether pilocarpine or *isopilocarpine* is selected as the initial material. Consequently the isomerism cannot exist in the complex $\begin{array}{c} \text{C}_2\text{H}_5 \cdot \text{CH} \cdot \text{CH} \cdot \text{CH}_2 \cdot \\ | \quad | \\ \text{CO} \quad \text{CH}_2 \\ \diagdown \quad / \\ \text{O} \end{array}$, but must be

in the glyoxaline ring, $\begin{array}{c} \cdot \text{C} \cdot \text{N}(\text{CH}_3) \\ || \quad | \\ \text{HC} \text{---} \text{N} \end{array} \text{CH}.$ "

Pinner's argument, therefore, is that if the isomerism is in the $\text{C}_7\text{H}_{11}\text{O}_2$ complex one ought to obtain isomeric homopilopic and pilopic acids corresponding to pilocarpine and *isopilocarpine*. Whereas both alkaloids yield on oxidation the same homopilopic acid. But this fact is readily explained when it is considered that the homopilopic or pilopic acid is formed in the presence of alkali, and is purified by the

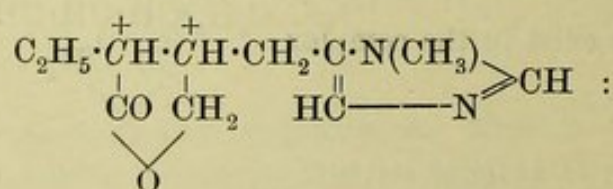
distillation of its ester, both of which conditions would ensure conversion into the *iso*-form.

The only valid argument against stereoisomerism and in favour of structural isomerism seems to be the apparent difference in the behaviour of the alkaloids towards bromine at 100°, but the explanation offered for this appears to be satisfactory. However, more experimental evidence on this point is desirable, and the investigation of the action of bromine under similar conditions on the different dimethylglyoxalines should throw some light on the subject, and this inquiry is already in hand.

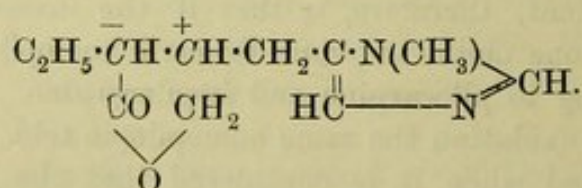
There seemed to be one experiment which would almost settle the question of the nature of the isomerism. If the alkaloids are stereoisomerides, then the conversion of pilocarpine into *isopilocarpine* should not be complete, but a state of equilibrium should result. By acting on *isopilocarpine* under the conditions which convert pilocarpine into *isopilocarpine*, for example, heating with alkali, the same state of equilibrium should be formed, and it should then be possible to isolate some pilocarpine from this mixture.

If, on the other hand, the alkaloids are structural isomerides, this reverse change should not be possible. For it must be assumed that one isomeride, namely, *isopilocarpine*, is the more stable under the conditions of experiment, and, as no possibility seems to exist for tautomerism, then this more stable isomeride could not pass into a less stable one by the reagent which has already produced the more stable isomeride.

This experiment would therefore appear to definitely settle the question, for if *isopilocarpine* could not be converted by alkali into pilocarpine then the isomerism cannot be solely stereochemical, but if this conversion does take place, then structural isomerism is extremely improbable, and the isomerism must be due to the racemisation of the asymmetric carbon atom adjacent to the carboxyl group. The relation between the alkaloids might thus be represented as follows :



Pilocarpine.



*iso*Pilocarpine.

A quantity of pure *isopilcarpine* nitrate (m. p. 159° ; $[\alpha]_D + 35.7^{\circ}$) was recrystallised from alcohol, and the mother liquors evaporated to a small bulk. The crystals which separated from the mother liquor melted at 159° , thus proving the homogeneity of the salt.

Fifty grams of the nitrate first mentioned were converted into the base, dissolved in alcohol, 30 grams of potassium hydroxide in alcoholic solution added, and the whole heated on a water-bath in a reflux apparatus for 3 hours. The base was regenerated and converted into the nitrate, which was then fractionally crystallised. The first fraction (40 grams) melted at 159° , and had $[\alpha]_D + 36.2^{\circ}$. It was therefore pure *isopilcarpine* nitrate.

From the mother liquors, two crops of crystals were obtained, both of which melted at 144° and had $[\alpha]_D + 58.7^{\circ}$. As the melting point of these two crops of crystals was not altered by recrystallisation, they were converted into the hydrochloride and then crystallised from absolute alcohol. After three recrystallisations, a product was obtained melting at 201° , and a determination of its specific rotation in water gave $\alpha_D + 1^{\circ}44'$; $l = 2$ dcm.; $c = 0.9336$; $[\alpha]_D + 92.8^{\circ}$.

Pilocarpine hydrochloride melts at 204° and has $[\alpha]_D + 91.7^{\circ}$.

In order to finally prove the identity of this substance with pilocarpine, the hydrochloride was converted into the nitrate. The nitrate melted at $177-178^{\circ}$, and the melting point was unchanged when mixed with an equal quantity of pilocarpine nitrate.

The first fraction obtained in the experiment was recrystallised, and then treated in the same manner with alcoholic potash, and a small quantity of pilocarpine nitrate (m. p. 176°) isolated from the resulting product.

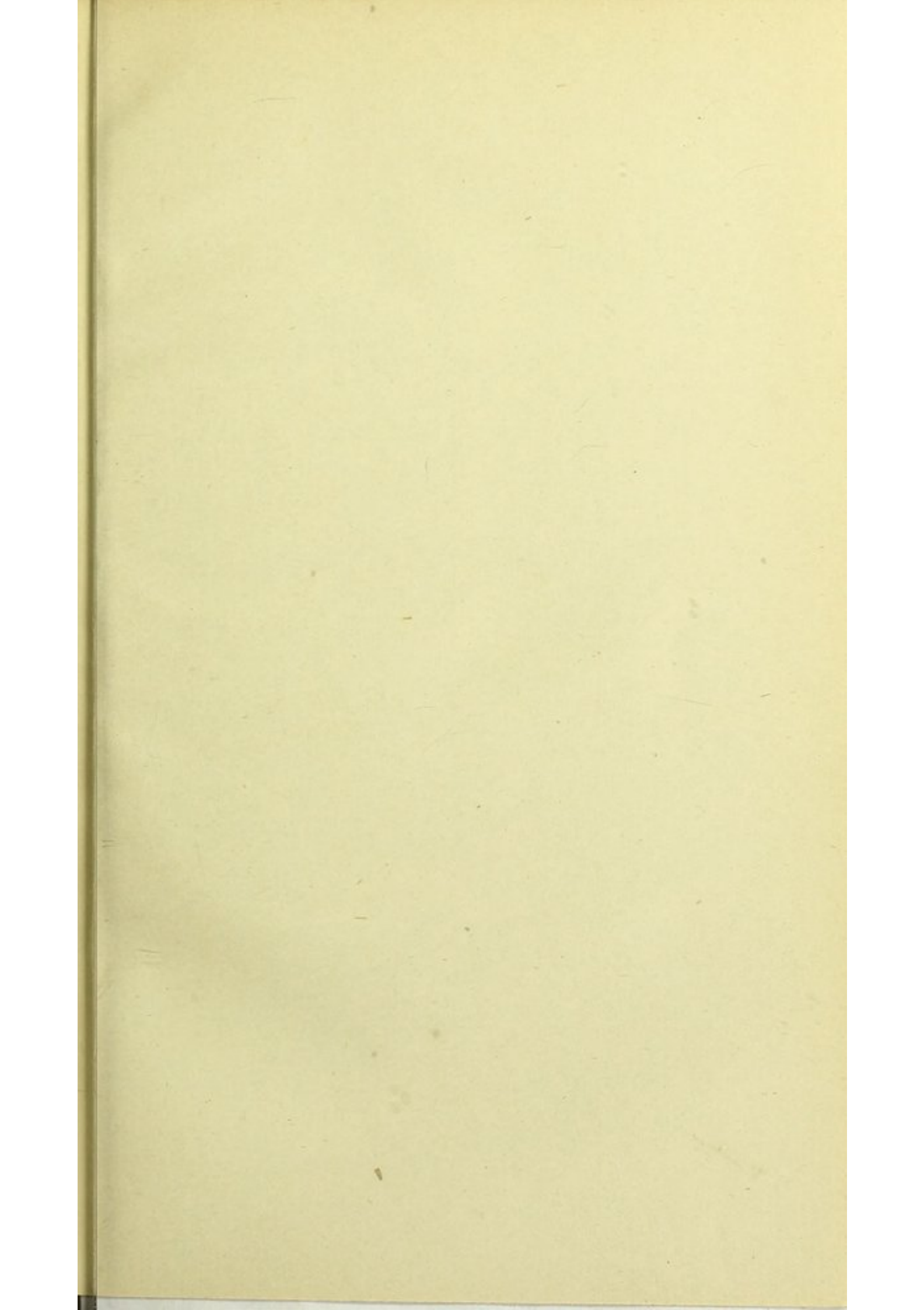
It was therefore absolutely proved that pure *isopilcarpine* nitrate, like pilocarpine nitrate, is converted by the action of alcoholic potash into an equilibrium mixture consisting chiefly of *isopilcarpine* with a small percentage of pilocarpine. This experiment therefore affords further evidence that pilocarpine and *isopilcarpine* are not structural isomerides but stereoisomerides.

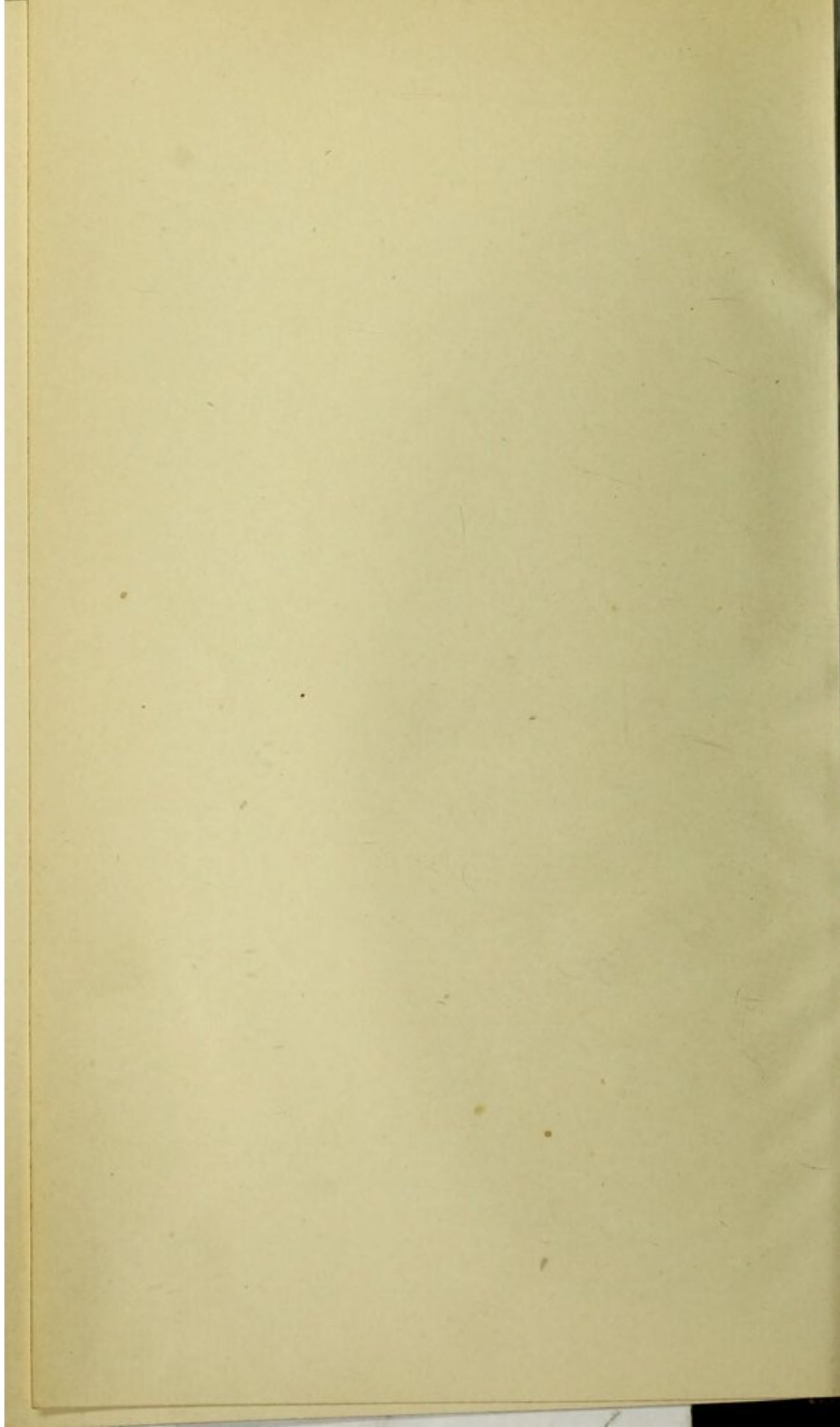
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FROM THE FIRST SETTLEMENT
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IN TWO VOLUMES
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OF THE BARR

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