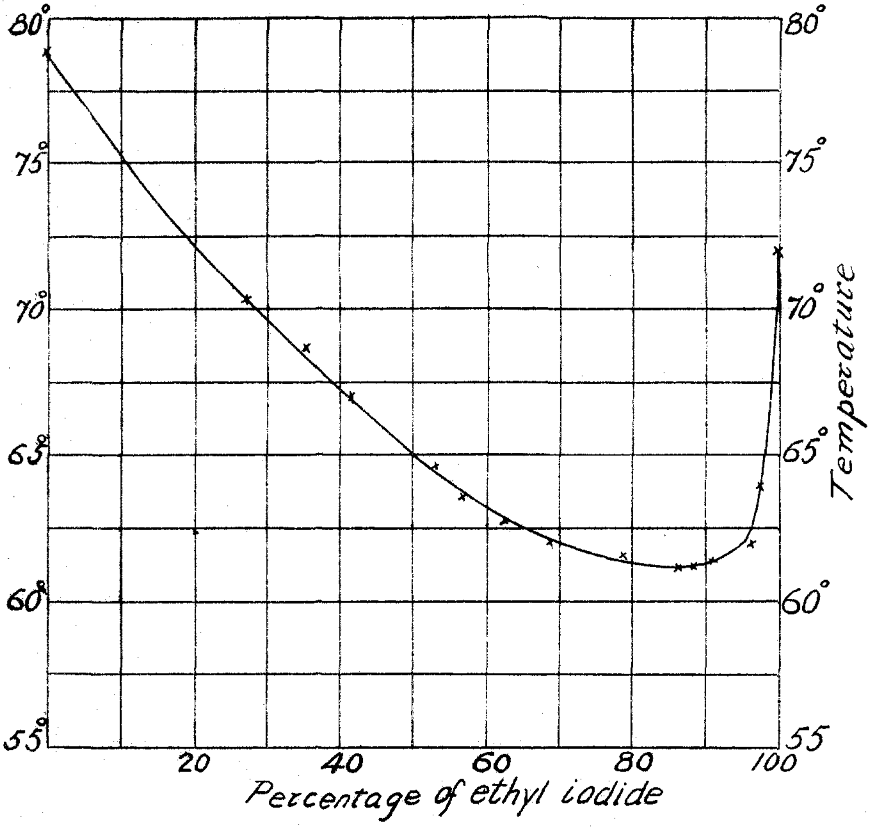

capillary measurements, the relation between boiling point and specific cohesion, and also from Traube's volume relations; but ethyl iodide is not an associating liquid.

CHEMICAL LABORATORY,
PRESIDENCY COLLEGE, CALCUTTA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS.]

MOLECULAR REARRANGEMENTS IN THE CAMPHOR SERIES. XII. DERIVATIVES OF ISOCAMPHORIC ACID; DECOMPOSITION PRODUCTS OF ISOAMINODIHYDROCAMPHOLYTIC ACID.[1]

BY WILLIAM A. NOYES AND LLOYD F. NICKELL.

Received November 26, 1913.

Of the four isomeric amino acids derived from *d*-camphoric acid and *l*-isocamphoric acid, the decomposition with nitrous acid of but one,

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[1] Abstract of a thesis presented by Lloyd F. Nickell in partial fulfilment of the requirement for the degree of Doctor of Philosophy at the University of Illinois.

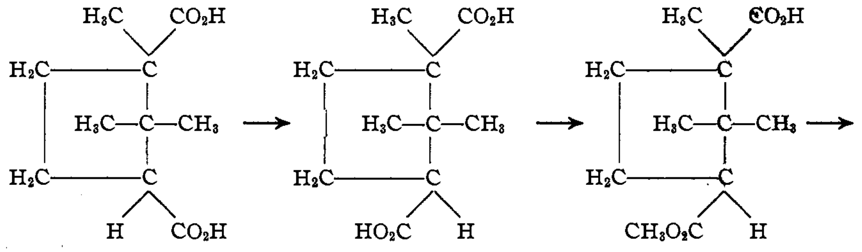
aminodihydrocampholytic acid, has been thoroughly studied. Noyes and Potter[1] decomposed this acid with nitrous acid and obtained the following products:

	Per cent.
Isolaurolene	0.7
d-Campholytolactone	5.3
l-Campholytic acid	12.0
d-*Trans*-hydroxydihydrocampholytic acid	45.0

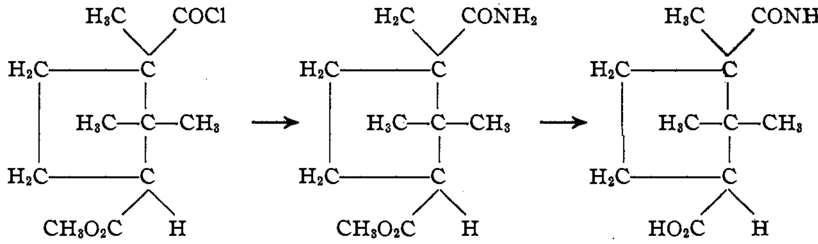
About 30% of the amino acid escaped decomposition.

The isomeric isoaminodihydrocampholytic acid has been prepared by Noyes and Knight[2] and its decomposition effected with nitrous acid. The study of the resulting products was far from complete, however. It was the aim of the present research to prepare the same compound, and investigate more completely the decomposition products formed with nitrous acid.

The isoaminodihydrocampholytic acid was prepared by the method of Noyes and Knight with some modifications. This method is indicated by the following:



d-Camphoric acid. *l*-Isocamphoric acid. α-Monomethyl ester of isocamphoric acid.[3]



β-Chloride of α-monomethyl isocamphoric ester. β-Amide of α-monomethyl isocamphoric ester. β-Isocamphoramidic acid.

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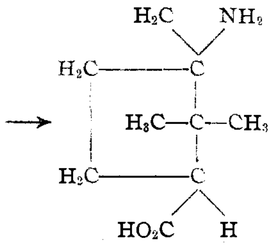
[1] THIS JOURNAL, 34, 1073.

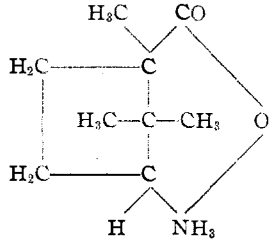
[2] *Ibid.*, 32, 1670.

[3] The secondary carboxyl is designated as α, the tertiary as β.



Isoaminodihydrocampholytic acid.

Free isoaminodihydrocampholytic acid was found to have a specific rotation, $[\alpha]_{\mathrm{D}}^{21°} = -39.9°$, and for its hydrochloride, $[\alpha]_{\mathrm{D}}^{19°} = -45.0°$. Both have the same sign of rotation. This is also true of aminodihydrocampholytic acid, ($[\alpha]_{\mathrm{D}} = +54.7°$) and its hydrochloride ($[\alpha]_{\mathrm{D}} = +41.3°$). For aminocamphonanic acid the reverse is true; for the free acid $[\alpha]_D = -29.2°$, and for its hydrochloride, $[\alpha]_D = +25.0°$. According to a view expressed by Noyes and Potter,[1] this indicates that aminocamphonanic acid forms an inner salt, thus:



while aminodihydrocampholytic acid does not. According to this view isoaminodihydrocampholytic acid does not form an inner salt in solution. This is to be expected from the fact that it is a *trans* compound. However, an intermolecular salt formation is indicated by an abnormally high molecular weight.

Decomposition of isoaminodihydrocampholytic acid with nitrous acid yields the following:

A hydrocarbon	small amount
d-Campholytic acid	35.8%
l-Campholytolacton	4.2%
l-Trans-hydroxydihydrocampholytic acid (impure)	19.1%

The formation of *d*-campholytic acid in the decomposition furnishes the first direct evidence that it is the secondary asymmetric carbon atom of *d*-camphoric acid that rearranges to form *l*-isocamphoric acid, and fully establishes this accepted view. The experimental evidence on this point thus far has been that Walker and Wood[2] by the electrolysis of the

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[1] Unpublished.

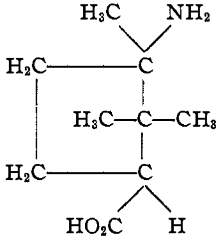
[2] *J. Chem. Soc.*, **77**, 387 (1900).

potassium salt of tertiary ethyl isocamphoric ester obtained the same product as in the electrolysis of the corresponding camphoric ester. Aschan,[1] who did not consider this evidence conclusive because the compounds prepared by Walker and Wood were evidently impure, obtained *l*-isocamphoric acid as well as *d*-camphoric acid by the reduction of bromocamphoric anhydride, which points to the same view.

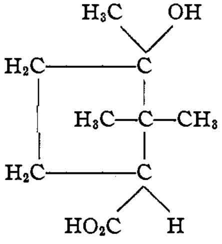
On the basis of Walker's results with campholytic acid, which led him to think that acid nearly or quite inactive, Aschan argues,[2] however, that the rearrangement occurs at the tertiary carbon atom. The fact, which had already been established by Noyes and Phillips,[3] but which had, apparently, been overlooked by Aschan, that campholytic acid has a high rotatory power, deprives this argument of its force. So far as we know, no one has discussed the question since Aschan's papers appeared. He considered the question as still open.

The hydroxy acid formed in this decomposition was regarded by Noyes and Knight as a *cis* compound, and they considered its formation as anomalous. Later it was shown[4] that the *d*-isomer was a *trans* acid. Hence this acid is *l*-*trans*-hydroxydihydrocampholytic acid and no inversion occurs in its formation above. In spite of this, the amount of the hydroxy acid formed is much less than the amount formed by inversion from the isomeric amino acid. On the other hand, the amount of the campholytic acid formed is very much greater.

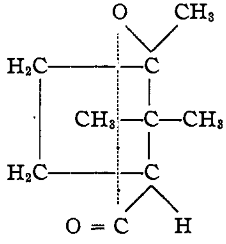
The structure and identity of *l*-campholytolactone were established from a comparison with the properties of *d*-campholytolactone. It can be formed from isoaminodihydrocampholytic acid only by a partial Walden inversion. These relations can be better understood from the following formulas:



Isoaminodihydrocampholytic acid.



l-*Trans*-hydroxydihydrocampholytic acid.



l-Campholytolactone.

In the decomposition of isoaminodihydrocampholytic acid the Walden inversion occurs to a very small extent, 1.8%, while in the decomposition of dihydroaminocampholytic acid it takes place to a much larger extent,

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[1] *Ann.*, **316**, 227 (1901).

[2] *Loc. cit.*

[3] *Am. Chem. J.*, **24**, 291 (1900).

[4] Noyes and Potter, *Loc. cit.*

45%. Since the iso-acid is a *trans* acid, and the aminodihydrocampholytic acid is a *cis* acid, and since the *trans* greatly exceeds the *cis* decomposition product in both cases, it is evident that the factor of "favored configuration" has an influence in the Walden inversion as encountered here.[1]

Experimental.

Preparation of l-Isocamphoric Acid.—Both the method of Marsh[2] and the method of Aschan[3] as modified by Noyes and Littleton[4] were tried. The latter method proved to be more satisfactory. It was carried out as follows: Eight sealed tubes each containing 100 grams of purified *d*-camphoric acid, 50 cc. of glacial acetic acid, and 5 cc. of hydrochloric acid (1.19) were heated in a bomb furnace at 175–180° for ten hours. Upon cooling, the viscous contents of the tubes were treated with three or four volumes of water. The mass was stirred frequently and in a half hour the greater part had crystallized. It was allowed to stand an hour longer, and was then filtered off. After drying on the water bath the pulverized material was thoroughly mixed with one-fourth its weight of acetyl chloride and allowed to stand for an hour. A quantity of water was added and the product filtered in order to remove the hydrochloric acid. The resulting mixture of *l*-isocamphoric acid and camphoric anhydride was separated by treatment with sodium bicarbonate solution. The isocamphoric acid was reprecipitated from the sodium bicarbonate solution and purified by dissolving in the smallest possible quantity of hot alcohol and reprecipitating by adding a quantity of hot water. The recovered anhydride was used in the next run. The yield of isocamphoric acid was one-third of the weight of camphoric acid used. As the anhydride was used again, no loss of material resulted.

Preparation of the α-Monomethyl Ester of Isocamphoric Acid.—The method of Noyes and Knight[5] was used to prepare this ester. The conditions, however, were more accurately regulated A solution of 100 grams of pure *l*-isocamphoric acid in 400 cc. of acetone-free methyl alcohol was heated to boiling in the water bath. Forty cc. of concentrated sulfuric acid were then added and the boiling continued for a half hour. The excess of methyl alcohol was rapidly distilled off under diminished pressure. The sirup-like residue solidified on the addition of water. The solid mass was filtered off and dissolved in sodium bicarbonate solution. The solution was extracted with ether to remove the diethyl ester, and the acid ester reprecipitated by the addition of hydrochloric acid. The raw product was recrystallized from petroleum ether (b. p. = 65–66°). The

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[1] See Noyes and Potter, THIS JOURNAL, 34, 1070 (1912).

[2] *Chemical News*, 60, 307.

[3] *Ber.*, 27, 205.

[4] THIS JOURNAL, 35, 77.

[5] *Loc. cit.*

product melted at 88°. 100 grams of isocamphoric acid gave 80 grams of the pure acid ester.

Preparation of the β-Amido-α-methyl Isocamphoric Ester.[1]—The use of an indifferent solvent in preparing the chloride in the following method was suggested by the work of Haller[2] and of Bredt:[3]

To 20 grams of powdered phosphorus pentachloride, covered with 75 cc. of ligroin (b. p. 25–40°), 20 grams of α-monomethyl isocamphoric ester were added, and the mixture allowed to stand until the reaction was complete. The reaction flasks were provided with return condensers and the contents protected from the atmosphere with calcium chloride. Two or three hours were required for complete action. A clear solution finally resulted.

The chloride was not isolated, the ligroin solution being used directly to prepare the amide. The above solution was added dropwise to 100 cc. of ammonia water (sp. gr. = 0.90) which was cooled in a freezing mixture and stirred vigorously with a mechanical stirrer. The amide precipitated out during this process and was filtered off After drying on the water bath the raw product gave a melting point of 157°. Recrystallization by dissolving in a small amount of alcohol and reprecipitating with water did not change this melting point but removed a small amount of ammonium chloride present in the raw material. Twenty grams of acid ester gave 16 grams of the amide ester.

Saponification of the Amide Ester.—The method given by Noyes and Knight[4] for the saponification of the amide ester, yielded, on acidifying the saponified product, an amorphous, putty-like mass that did not become crystalline, even on standing for a week. This product was afterward found to contain 6 to 10% of *d*-camphoric imide.

With the following modified method, however, a crystalline product was obtained. Thirty grams of β-amido-α-monomethyl isocamphoric ester were dissolved in 75 cc. of 95% alcohol. 1.1 mol of 30% sodium hydroxide solution was added, and the mixture allowed to stand on the water bath over night. The alcohol was distilled off under diminished pressure. The viscous residue was dissolved in 75 cc. of water and carbon dioxide passed into this solution for an hour. 1.7 grams of *d*-camphoric imide precipitated and was filtered out. This was identified by its melting point, 244°, which remained unchanged when it was mixed with some of the imide prepared in another manner and by the specific rotation, $[\alpha]_D = 8.9°$ in a 10% solution in absolute alcohol, the specific rotation of the other imide being 8.1°.

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[1] The secondary carbon atom is designated by α, and the tertiary carbon atom by β.

[2] *Bull. soc. chim.*, 70, 984 (1896).

[3] *Ber.*, 45, 1424.

[4] THIS JOURNAL, 32, 1671.

On acidifying the filtrate from the imide, there was precipitated an amorphous mass that quickly became crystalline. After drying, the melting point was 160°. After one recrystallization from dilute alcohol it melted at 165°.

The β-amido-α-monomethyl isocamphoric ester was tested for *d*-camphoric imide, but none was found. The imide was therefore formed during the saponification. Its formation involves, of course, the shifting of the carboxyl group from the *trans* to the *cis* side of the ring with reference to the tertiary carboxyl and the shifting of a hydrogen atom in the opposite direction.

Preparation of the Hydrochloride of Isoaminodihydrocampholytic Acid.—19.9 grams of the β-isocamphoramidic acid were dissolved in 100 cc. of 10% sodium hydroxide. To this solution there were added slowly 140 cc. of a 10% sodium hydroxide solution into which 5.1 cc. of bromine had recently been aspirated. The temperature rose to 45°. When the temperature began to fall the solution was put on the water bath and kept at 75° for a half hour. After cooling, 1 cc. excess of hydrochloric acid (1.1) was added, and the solution evaporated to a small volume under reduced pressure. One mol of hydrochloric acid (1.19) was added and the hydrochloride separated from the sodium chloride by fractional recrystallization. Two recrystallizations from water gave a fairly pure product. Yield, 23 grams. A pure product was obtained by dissolving in absolute alcohol and precipitating with ether.

Found, 17.28% Cl; Calculated for $C_8H_{14}(CO_2H)NH_2HCl$, 17.09%.
One gram dissolved in 10 cc. of water gave a specific rotation $[\alpha]_D^{19°} = —45.8$.

The chloride melts at 296–298° with decomposition.

Isoaminodihydrocampholytic Acid.—The hydrochloride was exactly neutralized with sodium hydroxide and the free acid precipitated by adding a large excess of acetone. By precipitating this product twice from water solution with acetone a pure product melting at 235–236° was obtained. Noyes and Knight[1] found 225–227° for an impure product.

One gram of the acid in 10 cc. of water gave a specific rotation, $[\alpha]_D^{21°} = —32.9°$.

Two molecular-weight determinations by the equilibrium method gave the following:

	Wt. of solution.	Wt. of acid.	T_F.	M(found).	M(theory).
I...........	23.292 grams	1.0151 gram	0.439°	192	171
II...........	19.151 grams	1.2741 grams	0.692°	190	...

The amphoteric nature of the substance evidently caused association in solution.

The Anhydride of Isoaminodihydrocampholytic Acid.—Distillation of

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[1] *Loc. cit.*

the hydrochloride with lime does not yield an anhydride.[1] Heating a mixture of the hydrochloride, fused sodium acetate, and acetic anhydride for forty minutes with a free flame yielded an anhydride that was identical with the anhydride of aminodihydrocampholytic acid. Less vigorous conditions gave no anhydride.

The specific rotation found for the anhydride was, $[\alpha]_D = +74.2°$; 1 gram in 10 cc. of absolute alcohol. That of the anhydride prepared from *d*-aminodihydrocampholytic acid was +73.2°. The melting point was 191°, that of the anhydride from *d*-aminodihydrocampholytic acid was 188°, while the mixture melted at 189°.

The formation of the anhydride involves the shifting of the secondary carboxyl group from the *trans* to the *cis* side of the ring with respect to the amino group. This is in marked contrast to *d*-transhydroxydihydrocampholytic acid, which forms a *trans* lactone without shifting of the carboxyl group.[2] It seems a little remarkable that heating with acetic anhydride at a temperature below 150° should cause this rearrangement when heating with lime at a much higher temperature does not do so.

Decomposition of Isoaminodihydrocampholytic Acid with Nitrous Acid.—51.7 grams (0.25 mol) of the hydrochloride of isoaminodihydrocampholytic acid were dissolved in 150 cc. of water. 22.5 grams of solid sodium nitrite were added to the solution and the mixture kept at 10° for an hour. At the end of this time decomposition had nearly ceased. Three cc. of sulfuric acid (sp. gr. = 1.3) were then added and the whole allowed to come to room temperature. One cc. excess of 30% sodium hydroxide solution was added and 75 cc. of distillate distilled with steam to remove the hydrocarbon. The residue was acidified and extracted with ether. Upon evaporating the ether a thick sirup remained. This residue was distilled with steam until the distillate became clear. The distillate was extracted with ether. Evaporation of the ether gave a yellowish, oily residue consisting of an unsaturated acid and a lactone.

The unsaturated acid and lactone were separated by means of potassium carbonate solution. The weight of the lactone was 1.8 gram, that of the unsaturated acid, 15.4 grams.

The residue from the steam distillation consisted of a brown tar which contained the hydroxy acid and weighed 8.2 grams.

Purification of the Lactone.—The lactone was crystallized twice from petroleum ether. It was a white, waxy substance melting at 114–115°. Further recrystallization did not change the melting point. A sample of pure *d*-campholytolactone melting at 114–115° was mixed with this

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[1] Both aminodihydrocampholytic acid and the chloride of aminocamphonanic acid ("aminolauronic acid"), which are *cis*-compounds, give an anhydride by this treatment. *Am. Chem. J.*, **16**, 504, 507.

[2] Noyes and Potter, THIS JOURNAL, 34, 1074 (1912).

lactone, and the mixture melted at 114–115°, 0.8528 gram of the lactone dissolved in 10 cc. of absolute alcohol gave a specific rotation $[\alpha]_D =$ —8.2°. *d*-Campholytolactone has a specific rotation, $[\alpha]_D^{24°} = +8.5°$. This shows the new lactone to be *l*-campholytolactone.

Hydrolysis of l-Campholytolactone; l-cis-Hydroxydihydrocampholytic Acid.—Seven tenths of a gram of *l*-campholytolactone and 2 cc. of 10% sodium hydroxide solution (1.25 mol) were heated on the water bath for three hours. The solution was acidified with hydrochloric acid and allowed to stand over night. Long, needle-like crystals were deposited. These were purified by dissolving in ether and reprecipitating by the addition of petroleum ether. The substance was an acid melting at 117–118°. It was mixed with a sample of *d-cis*-hydroxydihydrocampholytic acid, and the mixture melted at 117–118°. 0.3352 gram in 10 cc. of absolute alcohol gave a specific rotation, $[\alpha]_D = -53.1°$. *d-cis*-Hydroxydihydrocampholytic acid has a specific rotation, $[\alpha]_D = 50.8°$ and a melting point of 118.5°. The acid obtained by hydrolysis of *l*-campholytolactone is therefore *l-cis*-hydroxydihydrocampholytic acid.

The formation of this lactone and acid involves a shifting of the methyl and hydroxyl groups each to the opposite sides of the ring while the carboxyl group, and hydrogen atom retain their positions. This is in marked contrast with the conduct of the amino acid given above.

Purification of the d-Campholytic Acid.—The unsaturated acid obtained from the nitrous acid decomposition above was fractionally distilled with steam. The first fraction gave the highest specific rotation, $[\alpha]_D^{26°} = +66.35°$. Its density was 1.006 at 25°/25°. *l*-Campholytic acid has a specific rotation, $[\alpha]_D = -70.0$[1] and its density is 1.010. The new unsaturated acid is consequently *d*-campholytic acid.

As a further proof of its identity the acid was analyzed.

Calculated for $C_8H_{13}COOH$: C, 70.09; H, 9.16.
Found: C, 70.13; H, 9.34.

0.7633 gram required 9.98 cc. of half-normal alkali for naturalization as against 9.91 cc. for the theory.

Preparation of Racemic Campholytic Acid.—Two-tenths of a gram each of *l*- and *d*-campholytic acid were mixed. On standing at —17° for an hour the mixture solidified. The product dried on a porous plate melted at 31–32°. By recrystallizing from petroleum ether to constant melting point it melted at 37.8°. A similarly purified sample of *r*-campholytic acid prepared from inactive camphor melted at 40.5°. A mixture of the two melted at 38.0°. The identity of the unsaturated acid was thus established beyond question.

d-Trans-hydroxydihydrocampholytic Acid.—The tarry hydroxy acid crystallized with great difficulty. Only a few crystals were obtained.

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[1] Noyes and Potter, THIS JOURNAL, 34, 1077 (1912).

These melted at 132°. Since this acid has already been fully characterized,[1] the experiment was not repeated.

The hydrocarbon was obtained in an amount too small for study, its presence being indicated by the odor. It was doubtless isolaurolene.

Summary.

In conclusion the results of this investigation may be stated as follows:

1. The method of preparing isoaminodihydrocampholytic acid has been improved.
2. The free acid and the hydrochloride have been studied. The physical constants have been determined. A trans anhydride is not formed when the hydrochloride is heated with acetic anhydride and sodium acetate, but a rearrangement occurs to form the anhydride of the isomeric-*d*-aminodihydrocampholytic acid.
3. Decomposition of isoaminodihydrocampholytic acid with nitrous acid yields a hydrocarbon, *d*-campholytic acid, and *l*-*trans*-hydroxydihydrocampholytic acid. The Walden inversion occurs to only a slight extent in this decomposition, owing, probably, to a favored configuration.
4. A direct proof of the relation of *l*-isocamphoric acid to *d*-camphoric acid has been obtained.

URBANA, ILLINOIS.

THE DETERMINATION OF OXYGEN IN ORGANIC COMPOUNDS.

[SECOND PAPER.]

BY MAITLAND C. BOSWELL.

Received October 20, 1913.

A direct method for the determination of oxygen in organic compounds was described in the first paper of this series.[2] In the case of compounds of high oxygen content this gives satisfactory results, but if the oxygen is less than 30–40%, depending on the nature of the compound, the results are too high. In some cases, as anthraquinone, the results exceed the true value to the extent of several per cent., owing to the formation of reaction products other than water and carbon dioxide, which condense in the absorption apparatus. The method can hence be used with security only in the case of compounds containing at least 40% of oxygen. The present paper describes a method applicable to compounds, irrespective of the amount of oxygen present in them. It consists in heating a weighed quantity of substance in a quartz combustion tube in a current of nitrogen, causing the vapors to pass over a small quantity of heated copper oxide of known oxidizing value distributed over a long layer of asbestos, weighing the water and carbon dioxide formed, and determining the oxidizing

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[1] Noyes and Knight, *Loc. cit.*

[2] *J. Am. Chem. Soc.*, 35, 284 (1913).