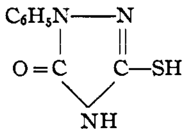
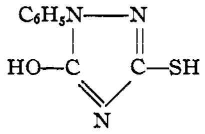
Conclusions.

From the chemical and conductivity data we can conclude that 1-phenyl-3-thiourazole exists in solution chiefly as an equilibrium mixture represented below:





By means of acids at 125°, under pressure, an alkyl mercaptan can be split off from the products obtained by methylating or ethylating 1-phenyl-3-thiourazole. Hence the assumption that the alkyl group is attached to the sulfur at position 3 seems substantiated further.

Since we obtain *very soluble* acids, apparently sulfinic and sulfonic acids on oxidizing 1-phenyl-3-thiourazole, but obtain *insoluble* sulfone-like substances having two additional oxygen atoms on the oxidation of the alkylation products assumed to be 1-phenyl-3-thioalkylurazoles and 1-phenyl-3-thioalkyl-4-alkylurazoles, we may conclude that these alkyl derivatives have an alkyl on the sulfur at 3, and not on the nitrogen at 2, and that 1-phenyl-3-thiourazole is alkylated in the tautomeric thioenol forms given above.

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BALTIMORE, MD.

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

THE VALENCE OF NITROGEN IN AMMONIUM SALTS.

BY WILLIAM A. NOYES AND RALPH S. POTTER.[1]

Received November 18, 1914.

During the early years of the development of the theory of valence, many chemists held the view that each element has an unvarying valence. The apparent change of valence in nitrogen from ammonia to ammonium salts, and in phosphorus from phosphorus trichloride to phosphorus pentachloride was explained by calling the ammonium salts and the pentachloride molecular compounds, as distinguished from ammonia and the trichloride, in which the true valence of the elements was supposed to be shown. This view received support from the dissociation of ammonium salts and of phosphorus pentachloride in the gaseous state. Gradually, with the demonstration that phosphorus pentachloride volatilizes in part unchanged, that phosphorus pentafluoride, PF_5, has a vapor density corresponding to its formula and, in general, that dissociation in the gaseous

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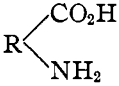
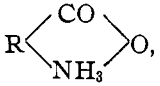
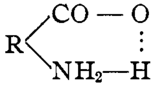
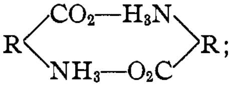
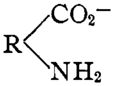
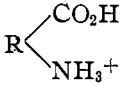
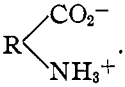
[1] Presented in abstract before the American Philosophical Society, April 24, 1914. This paper is also an abstract of a thesis presented to the Graduate Faculty of the University of Illinois in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

state does not correspond to any rational distinction between unitary and molecular compounds, the view that elements may show a varying valence in their compounds and that nitrogen and phosphorus are sometimes trivalent and sometimes quinquivalent, come to be generally accepted.

More recently, Werner[1] has proposed a modified molecular formula for ammonium chloride, $H_3N\cdots HCl$. By this formula he intends to indicate that in the ammonium salts the nitrogen atom retains a normal valence of three, but that the nitrogen atom of the ammonia and the hydrogen atom of the hydrochloric acid are held together by secondary ("Neben") valences, the hydrogen and chlorine of the acid retaining essentially the same relation to each other as in the free acid.

An amino acid may, theoretically, assume in the aqueous solution the following forms: *a*, the free acid,  $R\left\langle\begin{matrix}CO_2H\\NH_2\end{matrix}\right.$; *b*, a cyclic salt, , or according to Werner, ; *c*, a bimolecular or polymolecular salt formed by the union of two or more molecules, ; *d*, the ions of the acid group  $R\left\langle\begin{matrix}CO_2^-\\NH_2\end{matrix}\right.$ and H^+; *e*, the ions of the base,  $R\left\langle\begin{matrix}CO_2H\\NH_3^+\end{matrix}\right.$ and OH^-; *f*, the double, amphoteric ion,  $R\left\langle\begin{matrix}CO_2^-\\NH_3^+\end{matrix}\right.$.[2]

The "inner salt" structure was first proposed by Erlenmeyer and Siegel[3] in 1875. Ten years later Ostwald[4] noticed that solutions of glycocoll, $CH_2NH_2CO_2H$, have a very low molecular conductivity and that this is only slightly increased by dilution. He states that in its behavior it is more like a neutral salt than an acid. In 1891 Marckwald[5] called attention to the fact that amino acids of the aliphatic series react only slowly with the mustard oils, while other primary amines react quite readily. Since the amino acids react easily in alkaline solutions, he held that the acids are, in reality, inner salts. Sakurai[6] attempted to substantiate the "inner salt" structure on their preparation from halogen derivatives of the acids and on the resistance which amino acids offer to the formation of acid chlorides. Walker[7] points out that conductivity determinations

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[1] See *Neuere Anschauungen auf dem Gebiet der anorganischen Chemie*, **1905**, p. 96.

[2] "Zwitterion."

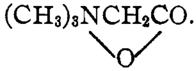
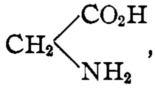
[3] *Ann.*, **176**, 349 (1875).

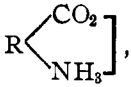
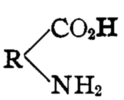
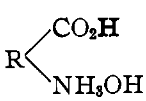
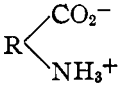
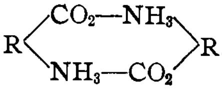
[4] *J. prakt. Chem.*, **32**, 369 (1885).

[5] *Ber.*, **24**, 3278 (1891).

[6] *Proc. Chem. Soc.*, **10**, 90 (1894).

[7] *Ibid.*, **10**, No. 139 (1895).

tell us very little about the structure of glycocoll, but that, since the conductivity of phenylglycocoll, $C_6H_5NHCH_2CO_2H$, is greater than that of acetic acid, it must contain a carboxyl group which ionizes. Tilden and Forster[1] showed that the amino group of amino acids may be replaced by chlorine by the action of nitrosyl chloride, and considered this an argument against the inner salt formation. Somewhat later Carrara and Rossi[2] based an argument for the inner salt structure on the conductivity of betaine hydrochloride, $(CH_3)_3NClCH_2CO_2H$. From the values found they considered that the salt was almost completely hydrolyzed to hydrochloric acid and betaine,  $(CH_3)_3\underset{\diagdown O \diagup}{NCH_2CO}$. Winkelblech[3] points out, however, that if betaine hydrochloride is in reality hydrolyzed the conductivity of the solution should be the same as that of the equivalent amount of hydrochloric acid, while both Bredt's measurements and those of Carrara and Rossi gave a conductivity scarcely more than one-half as great. There can be no doubt, of course, that the anhydride of betaine, $(CH_3)_3NCH_2CO_2$, has the structure of a salt, but no one seems to have determined whether this is monomolecular or dimolecular. Walker[4] has shown, however, that aminoacetic acid,  $CH_2\Big\langle\begin{matrix}CO_2H\\NH_2\end{matrix}$, is monomolecular in aqueous solutions. Our results, given below, indicate that a solution of an amino acid which gives no inner salt may still contain the acid mostly in the monomolecular form.

Winkelblech[5] discusses the hydrolysis of an amino acid on the basis of conductivity data for weak acids, weak bases and water. It does not seem possible from conductivity data, however, to determine whether the acid is in the form of an inner salt,  $R\Big\langle\begin{matrix}CO_2\\NH_3\end{matrix}\Big]$, in the unionized state,  $R\Big\langle\begin{matrix}CO_2H\\NH_2\end{matrix}$ or  $R\Big\langle\begin{matrix}CO_2H\\NH_3OH\end{matrix}$, in the form of the double, amphoteric ion  $R\Big\langle\begin{matrix}CO_2^-\\NH_3^+\end{matrix}$, or in the form of a bimolecular salt,  $R\Big\langle\begin{matrix}CO_2-NH_3\\NH_3-CO_2\end{matrix}\Big\rangle R$. The hydrogen and hydroxyl ions of the amphoteric form would, of course, combine to form water and if the acid and basic functions were of equal "strength" the solution would react neutral. None of these forms would show any conductivity and, while the bimolecular form could be disting-

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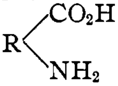
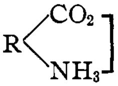
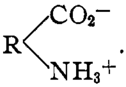
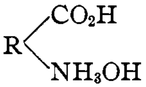
[1] *Chem. News*, 71, 239 (1895).

[2] *Atti R. Accad. Lincei*, [5] 6, 208 (1897).

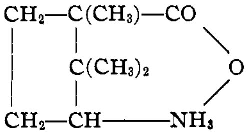
[3] *Z. physik. Chem.*, 36, 590 (1901).

[4] *Proc. Chem. Soc.*, 10, 94 (1894).

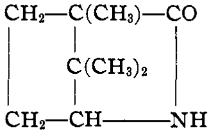
[5] *Loc. cit.*

uished from the others by a determination of the molecular weight, it is not clear how any of the ordinary physical methods could be used to distinguish between the three forms,  , , and . The form  would have a higher molecular weight and might, possibly, be distinguished from the other three by that means, but it could not be distinguished by conductivity measurements. It does not seem to us that the ordinary equations for hydrolysis, which Winkelblech attempts to apply, could be used in a complex case of this sort.

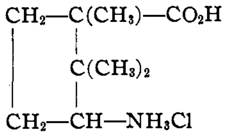
From the above summary it would seem that the evidence with regard to inner salt formation is not altogether satisfactory and light upon the question from an entirely different point of view is welcome. We think that we have secured this from a study of the specific rotations of a series of amino acids from camphor. The formulas and names of the compounds are given below. To bring out the relationships more clearly the specific rotations given for the salt are calculated to the basis of one gram of the free acid in 1 cc. of the solution instead of for one gram of the salt.



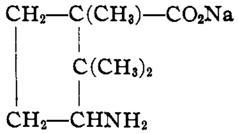
Aminocamphonanic Acid. $[\alpha]_D = -29.2°$.



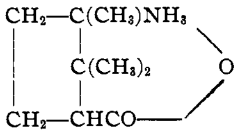
Anhydride of Aminocamphonanic Acid. $[\alpha]_D = -60.5°$.



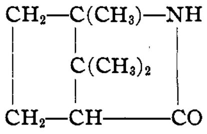
Hydrochloride of Aminocamphonanic Acid. $[\alpha]_D = 25.0°$.



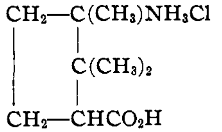
Sodium Salt of Aminocamphonanic Acid. $[\alpha]_D = 52.8°$.



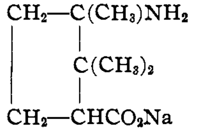
Aminodihydrocampholytic Acid. $[\alpha]_D = 53.7°$.



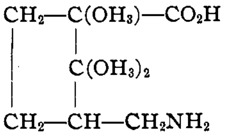
Anhydride of Aminodihydrocampholytic Acid. $[\alpha]_D = 72.8°$.



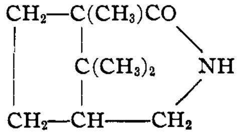
Hydrochloride of Aminodihydrocampholytic Acid. $[\alpha]_D = 41.3°$.



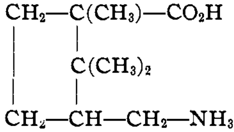
Sodium Salt of Aminodihydrocampholytic Acid. $[\alpha]_D = 18.3°$.



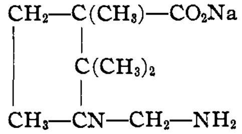
α-Aminocampholic Acid. $[\alpha]_{\mathrm{D}} = 67^\circ$.



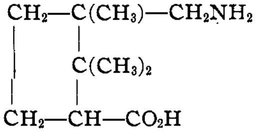
Anhydride of α-Aminocampholic Acid (α-Camphidone). $[\alpha]_{\mathrm{D}} = -33.9^\circ$.



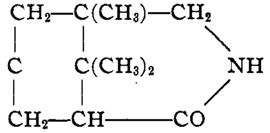
Hydrochloride of α-Aminocampholic Acid. $[\alpha]_{\mathrm{D}} = 44.7^\circ$.



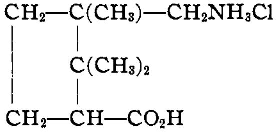
Sodium Salt of α-Aminocampholic Acid. $[\alpha]_{\mathrm{D}} = 62.4^\circ$.



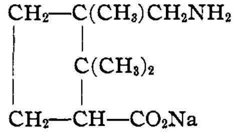
β-Aminocampholic Acid. $[\alpha]_{\mathrm{D}} = 16.4^\circ$.



Anhydride of β-Aminocampholic Acid (β-Camphidone). $[\alpha]_{\mathrm{D}} = 66.5^\circ$.



Hydrochloride of β-Aminocampholic Acid. $[\alpha]_{\mathrm{D}} = 41.3^\circ$.

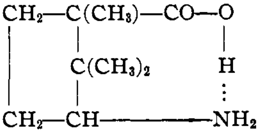


Sodium Salt of β-Aminocampholic Acid. $[\alpha]_{\mathrm{D}} = 14.3^\circ$.

It will be noticed that the aminocamphonanic acid and aminodihydrocampholytic acid are represented as having a cyclic or inner salt structure, while the aminocampholic acids are both represented as having an open structure. The evidence for these structures is based on the specific rotation of the compounds. The rotation of the sodium salt and hydrochloride of aminocamphonanic acid are to the right while that of the anhydride, which is undoubtedly cyclic in structure, is to the left. The ammonium salt is also left handed, indicating a cyclic structure similar to that of the anhydride. The sodium salt and hydrochloride of aminodihydrocampholytic acid are right handed. The free acid and anhydride are also right handed, but with a considerably increased rotation. The sodium salt and free α-aminocampholic acid are both right handed with rotations closely alike, indicating that each has an open structure, but the anhydride, which certainly has a cyclic structure, is left handed and has a rotation very closely like that of the aminocamphonanic acid, indicating again very clearly that the latter has a cyclic structure and that each *compound contains a cycle of six atoms.* The sodium salt of β-aminocampholic acid and the free acid also correspond closely in rotation, indicating an open structure for both, while the hydrochloride and anhydride have a considerably greater rotation, as is the case with both the free aminodihydrocampholytic acid and its anhydride.

All of these observations are consistent with the hypothesis that aminodihydrocampholytic and aminocamphonanic acid form cyclic salts containing cycles of six atoms, while the aminocampholic acids do not form such salts, because, if formed, they would contain cycles of seven atoms. It seems dfficult to find any other simple explanation for the observations.

The results also point very strongly to the formula for ammonium salts which represents them as containing quinquivalent nitrogen and against Werner's formula. According to Werner's formula the free aminocamphonanic and aminodihydrocampholytic acids would contain cycles of seven atoms,



Such a formula is quite inconsistent with all that we know about the ease with which rings of five and six atoms are formed and the comparative rarity of seven-atom rings. It is also inconsistent with the close agreement between the rotation of the aminocamphonanic acid and that of the anhydride of α-aminocampholic acid. We know that the latter compound contains a six-atom ring.

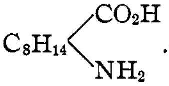
Determinations of the molecular weights in aqueous solutions by the freezing point method have shown that all four of the amino acids are monomolecular in such solutions.

The following table brings out in a striking way the relations which have been found. The rotations are calculated from results obtained with solutions containing from 2.5 to 10% of the substances examined and are given on the basis of the amount of free amino acid corresponding to the compound which was present. Thus $[\alpha]_D$ for the hydrochloride of aminocamphonanic acid (*i. e.*, the rotation in a 10 cm. tube of 1 g. in 1 cc.) is 25.0° but the rotation in the table is given as 30.3°, which is the calculated rotation for 1 g. of the free acid in 1 cc., after conversion into the hydrochloride.

	HCl salt.	Free acid.	HCl salt + 1 mol NaOH.	HCl salt + 2 mols NaOH.	Anhydride.
Aminocamphonanic acid............	30.3°	—29.2°	—28.8°	55.4°	—60.5°
Aminodihydrocampholytic acid......	50.1°	54.7°	54.0°	20.5°	72.8°
α-Aminocampholic acid.............	53.3°	67.0°	62.4°	65.6°	—33.9°
β-Aminocampholic acid.............	49.5°	16.4°	16.7°	15.2°	66.5°

The free acids have, in each case, nearly the same rotation when prepared by the addition of one mol of sodium hydroxide to one mol of the hydrochloride, as when the pure acid is dissolved directly in water. The addition of a second mol of sodium hydroxide causes a large change in the rotations of aminocamphonanic and aminodihydrocampholytic acids, evidently because the cyclic structure of the inner salt is broken down by the formation of the sodium salt, but no such change is observed with the campholic acids.

Experimental.

Aminocamphonanic Acid,  $C_8H_{14}\langle^{CO_2H}_{NH_2}$.—The hydrochloride of aminocamphonanic acid was prepared as previously described.[1] One hundred grams of the hydrochloride were dissolved in water and a solution of sodium hydroxide added till the reaction was faintly alkaline to phenolphthalein after boiling a small portion in a test tube. The solution was then evaporated to about 100 cc. and the free amino acid obtained was filtered off and was recrystallized by dissolving in water and evaporating the solution. The yield of the crude acid was 72 g., about 82% of the theory. It is possible to recover the remainder of the acid as hydrochloride from the mother liquors. The free acid is about equally soluble in hot and cold water. Hoogewerf and Van Dorp[2] report a melting point of 260°. If heated rather rapidly we find that it sublimes without melting at a temperature above 300°. It is probable that the melting point reported by Hoogewerf and Van Dorp was found by heating slowly, which causes a partial conversion into the anhydride. The latter melts at 203°. Because of the melting point reported by the authors mentioned, and because of the left-handed rotation, which seemed to us, at first, anomalous for a derivative of dextrocamphoric acid, the mother liquors from the preparation of the aminocamphonanic acid were very carefully examined for a possible isomer, but none was found.

The aqueous solution of aminocamphonanic acid, 10 g. in 100 cc. of the solution, gave a specific rotation $[\alpha]_D^{25°} = -29.2°$.

The molecular weight was determined with a sample which had been recrystallized six times from water, twice more than was necessary to remove all of the chlorine. A solution of the acid was mixed with ice, from distilled water, which had been broken to pieces the size of a pea and the mixture was placed in a Dewar bulb. After equilibrium was reached and the temperature had been taken, 20 cc. of the clear solution were drawn off and evaporated and the residue dried to constant weight on the water bath. The results were:

Subst., 0.304; H_2O, 16.6; depression, 0.194; mol. wt. found, 173. Calc. for $C_8H_{14}CO_2NH_3$, 171.

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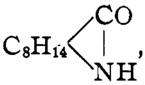
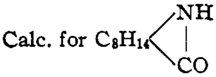
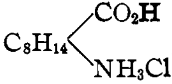
[1] *Am. Chem. J.*, **16**, 507 (1894). Formerly called aminolauronic acid. See THIS JOURNAL, **34**, 1067 (1912).

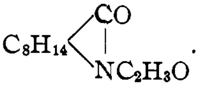
[2] *Ibid.*, **16**, 506 (1874), footnote.

The Anhydride of Aminocamphonanic Acid,  $C_8H_{14}\left\langle\begin{array}{l}CO\\ |\\ NH\end{array}\right.$, has been prepared[1] by distilling a mixture of the hydrochloride and lime. The following method gives a nearly quantitative yield and avoids the use of a high temperature: Ten grams of the hydrochloride, 6 g. (1.5 mol) of fused sodium acetate, and 20 cc. of acetic anhydride were boiled gently in a long necked flask for about 10 min. After cooling, 10% excess of a strong solution of sodium hydroxide was added and the mixture heated on the water-bath till the liquid layer which formed at first on top was changed to a solid. The liquid layer probably consisted in part of the acetyl derivative of the anhydride, but this was not examined further. After cooling, the anhydride was separated by two extractions with ether. After two crystallizations from petroleum ether it melted quite sharply at 203°.[2]

$[\alpha]_D^{29°} = -60.5$, 1 g. in 10 cc. of absolute alcohol and $[\alpha]_D^{28°} = -60.6°$, 0.05 g. in 10 cc. of water. Noyes and Taveau[3] found $[\alpha]_D^{26°} = -60.1°$ for a 10% alcohol solution.

Subst., 0.373, 0.750; H_2O, 20.9, 20.1; depression, 0.208°, 0.432°; mol. wt. found, 157, 159. Calc. for  $C_8H_{14}\left\langle\begin{array}{l}NH\\ |\\ CO\end{array}\right.$: 153.

Hydrolysis of Aminocamphonanic Acid Anhydride.—The anhydride was not hydrolyzed by heating with water for three days in a water-bath. Heating for three days in the water-bath with an excess of sodium hydroxide was also without effect, but when 3 g. of the anhydride were heated for 10 hrs. with 20% hydrochloric acid the solution deposited crystals of the hydrochloride of aminocamphonanic acid,  $C_8H_{14}\left\langle\begin{array}{l}CO_2H\\ NH_3Cl\end{array}\right.$, on cooling. This gave $[\alpha]_D^{24°} = 24.9°$, proving that there is no inversion of the acid either in the formation of the anhydride or in its hydrolysis.

Acetyl Derivative of Aminocamphonanic Anhydride,  $C_8H_{14}\left\langle\begin{array}{l}CO\\ |\\ NC_2H_3O\end{array}\right.$. —This was prepared by boiling a mixture of 6 g. of aminocamphonanic acid hydrochloride, 3.5 g. of sodium acetate and 12 cc. of acetic anhydride for 10 min. After cooling and adding enough sodium hydroxide to nearly neutralize the acetic acid and excess of acetic anhydride, the mixture was extracted with petroleum ether and the extract washed with water to remove free acid. After drying with sodium sulfate and distilling away the

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[1] This Journal, 34, 62 (1912).

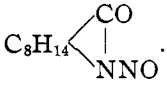
[2] *Am. Chem. J.*, 16, 507 (1894).

[3] *Ibid.*, 32, 288 (1904).

petroleum ether, a slightly yellow oil was obtained. This was distilled and the portion boiling at 260–262° was analyzed:

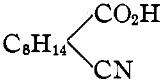
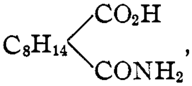
Calc. for $C_8H_{14}CONC_2H_3O$: N = 7.16; found: 7.05; $[\alpha]_D = +72.7°$, 0.544 g. in 5 cc. of alcohol.

The substance gave aminocamphonanic anhydride melting at 201–203° by hydrolysis with sodium hydroxides.

Nitroso Derivative of Aminocamphonanic Anhydride,  $C_8H_{14}\left<\begin{matrix}CO\\|\\NNO\end{matrix}\right.$. —This was prepared by Bredt,[1] but he did not determine the specific rotation.

We found $[\alpha]_D^{24°} = 153°$; 0.25 g. in 10 cc. of alcohol.

It is interesting to notice that both the acetyl and the nitroso group change the negative rotation of the anhydride to a positive, the nitroso group producing a much larger effect than the acetyl group.

Cyanocamphonanic Acid,  $C_8H_{14}\left<\begin{matrix}CO_2H\\CN\end{matrix}\right.$, was prepared by treating α-camphoramidic acid,  $C_8H_{14}\left<\begin{matrix}CO_2H\\CONH_2\end{matrix}\right.$, with acetyl chloride, according to the method of Hoogewerf and Van Dorp.[2] This gave about the same yield of crude acid which they obtained, namely, about 50%. It was thought, since the hydrochloride of the α-isoimide obtained by treating the α-camphoramidic acid with acetyl chloride is very easily hydrolyzed by water to the α-camphoramidic acid, that perhaps by suspending the isoimide hydrochloride in petroleum ether and passing in dry ammonia gas, the yield could be increased. The following procedure was used: 12.5 g. of α-camphoramidic acid and 50 g. of acetyl chloride were placed in a flask which was attached to a reflux condenser. The flask was heated on the water bath. A solution is first formed and in about two minutes the contents of flask apparently become solid. The flask and material were then cooled, the material filtered and the solid washed with carbon disulfide. Up to this point the method of procedure was just the same as given by the above mentioned investigators. Instead of adding the isoimide hydrochloride to 20% ammonia, as they did, it was shaken with petroleum ether and a slow stream of dry ammonia gas was passed through the mixture until saturation was reached. A dilute solution of ammonia was added to dissolve the ammonium salts, and from the aqueous solution the cyanoacid was precipitated with dilute hydrochloric acid. The hydrochloric acid solution must be added drop by drop or the cyanoacid will be precipitated as a gummy mass. The crystalline acid was filtered

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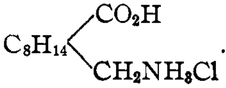
[1] *Ber.*, **35**, 1291 (1902).

[2] *Rec. trav. chim.*, **14**, 261 (1895).

and, after drying, was weighed. 10 g., or 84%, of the theory was obtained. For purification two methods were used, one by recrystallization from hot water, which was the method used by Hoogewerf and Van Dorp, the other, by dissolving the acid in dilute ammonium hydroxide and precipitating it with dilute hydrochloric acid. By the first method from 5 g. of the crude acid 2.4 g. of acid, melting sharply at 121°, were obtained. This is the melting point found by the above mentioned investigators. By the second method, 3.1 g. of the pure product were obtained from 5 g. of the crude acid. This method is also to be preferred on account of its greater ease of manipulation.

$[\alpha]_D^{26°} = 67.3°$, 1 g. in 10 cc. of alcohol. Hoogewerf and Van Dorp[1] found exactly the same for a 6% alcoholic solution.

α-Aminocampholic Acid Hydrochloride,  $C_8H_{14}\langle{}^{CO_2H}_{CH_2NH_3Cl}$.—The only variation from the method of preparation of Hoogewerf and Van Dorp[2] or Rupe and Splittgerber[3] was that a somewhat larger portion of sodium was used in the reduction. 5 g. of cyanocamphonanic acid were dissolved in 50 cc. of absolute alcohol and 15 g. of sodium were added in small portions, the flask being connected to a reflux condenser. During the addition of the sodium about 20 cc. more of alcohol were added. After all the sodium had dissolved water was added and the solution was evaporated until the odor of alcohol was no longer given. From this point on a method of separation and purification of the hydrochloride entirely different from that of Rupe and Splittgerber[3] was used. Hydrochloric acid in slight excess was added to the cold solution and it was then extracted with ether in order to remove any unchanged cyanoacid. Upon evaporation of the ether solution it was found that about 1 g. of cyanoacid was obtained. This was used in subsequent reductions. The hydrochloric acid solution was evaporated to dryness and the residue ground up in a mortar with alcohol. The alcohol was filtered, diluted, with water and the alcohol was evaporated. The brown turbidity of the solution was then removed by filtering twice through powdered animal charcoal. The clear solution was then evaporated on the water bath until crystals started to form, when it was removed and allowed to cool and filtered. The very slightly brown crystals were dissolved in the minimum amount of hot water, filtered again through animal charcoal and after cooling, the pure white, needle-like crystals were filtered off, dried, and a melting point taken. It was found to be 248–250°. A portion was again recrystallized and the same melting point was given.

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[1] *Rec. trav. chim.*, 14, 26 (1895).

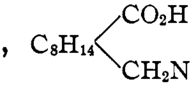
[2] *Ibid.*, 14, 261 (1895).

[3] *Ber.*, 40, 4313 (1907).

Rupe and Splittgerber[1] give the melting point as 247–248°. The specific rotation, which had never been taken before, was determined.

$[\alpha]_D^{24°} = 44.7°$; 0.5 g. in 10 cc. of a solution in water.

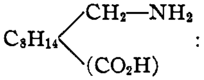
Calc. for $C_8H_{14}(CO_2H)CH_2NH_2HCl$: Cl = 16.00; found: Cl, 16.17.



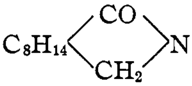
α-Aminocampholic Acid, $C_8H_{14}\left\langle\begin{array}{l}CO_2H\\CH_2NH_2\end{array}\right.$.—An attempt was made to prepare the free acid from its hydrochloride in the same manner that aminocamphonanic acid is prepared from its hydrochloride, but the free acid was apparently more soluble than sodium chloride and this method was abandoned. Instead, the hydrochloride was dissolved in water and sodium hydroxide added until an outside test with phenolphthalein showed a very faint alkaline reaction. The solution, after filtering, was evaporated to dryness and the residue was ground up in a mortar with alcohol, the alcohol filtered, diluted and partially evaporated. The slightly turbid solution was filtered through charcoal and then the solution was evaporated until only a few cubic centimeters of liquid were left, a large mass of crystals having separated during the evaporation. The crystals were filtered off and recrystallized by evaporation of the water solution, the acid being practically as soluble in cold as in hot water. This was repeated three times more and the acid then showed no trace of chlorine. The molecular weight was determined with this sample. Heated in a capillary tube no melting point was obtained but considerable decomposition took place between 300° and 320°, depending upon the rate of heating.

$[\alpha]_D^{26°} = 67.0°$; 0.207 g. in 10 cc. of solution.

Subst., 0.418, 0.585; H_2O, 15.6, 18.4; depression, 0.251°, 0.297°; mol. wt. found, 196, 197. Calc. for



$C_8H_{14}\left\langle\begin{array}{l}CH_2{-}NH_2\\(CO_2H)\end{array}\right.$: 185.



α-Camphidone, $C_8H_{14}\left\langle\begin{array}{c}CO\\CH_2\end{array}\right\rangle NH$.—This was prepared from the hydrochloride of α-aminocampholic acid in precisely the same manner as the anhydride of aminocamphonanic acid was prepared from the hydrochloride of aminocamphonanic acid. After making the acetic anhydride solution alkaline with sodium hydroxide the same liquid layer was observed on the surface that was observed in the preparation of the above mentioned anhydride. This was very likely the acetyl derivative, but no attempt was made to isolate it. Practically a theoretical yield of the anhydride was given. It melts at 229–231°. Recrystallizing once from petroleum ether gave a pure product melting at 230–231°.

$[\alpha]_D^{25°} = -33.9°$; 0.5 g. in 10 cc. alcohol solution. Rupe and Splittgerber[1] give $[\alpha]_D = -37.2°$ in a 10% solution in benzene.

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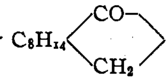
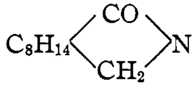
[1] *Ber.*, 40, 4313 (1907).



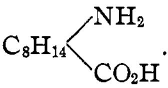
Calc. for $C_8H_{14}\left\langle\begin{matrix}CO\\CH_2\end{matrix}\right\rangle NH$: N = 8.38; found: N = 8.42.



Nitroso Derivative of α-Camphidone, $C_8H_{14}\left\langle\begin{matrix}CO\\CH_2\end{matrix}\right\rangle NNO$.—The α-camphidone was dissolved in hydrochloric acid (1 : 4) and a sodium nitrite solution slowly added. The yellow crystals formed were filtered, dried and recrystallized from hot alcohol. The lemon yellow, needle-like crystals gave a melting point of 125–126°. The product given by a second recrystallization showed the same melting point.

$[\alpha]_D^{23°} = -59.0°$; 0.25 g. in 10 cc. of alcohol.

From analogy to the well-known nitroso derivatives of aminocamphonanic and dihydroaminocampholytic acid anhydrides, it was not thought necessary to analyze the compound for identification.



Aminodihydrocampholytic Acid, $C_8H_{14}\left\langle\begin{matrix}NH_2\\CO_2H\end{matrix}\right.$.—This acid was prepared in the same manner as described by Noyes[1] except that a more elaborate method was followed in recovering the last traces of the acid. The procedure followed was identical with that for the preparation of aminocamphonanic acid from α-camphoramidic acid, except that β-camphoramidic acid was used and, instead of adding sufficient hydrochloric acid to give the acid hydrochloride, only enough was added to give a solution exactly neutral to phenolphthalein. After this point the solution was evaporated until the sodium chloride was starting to come down. The crystals of the amino acid were then filtered off and to the filtrate an excess of hydrochloric acid was added and the whole evaporated to dryness, and the residue extracted with alcohol. Since the dihydroaminocampholytic acid is quite easily esterified, the alcoholic solution was diluted with considerable water and just enough sodium hydroxide solution added to give a solution neutral to phenolphthalein. It was then partially evaporated and the amino acid filtered off. An excess of hydrochloric acid was added to this filtrate and the same procedure followed as above. Since the acid is no more soluble in hot than in cold water and is not soluble in any other solvent it must be purified by dissolving in water and partial evaporation. For ordinary purposes one recrystallization is sufficient. For taking the molecular weight and rotations an acid was used which had been recrystallized six times, two more times than was necessary to free it from traces of chlorine.

$[\alpha]_D^{25°} = 54.7°$; 0.5 g. in 10 cc. of water solution. Noyes and Phillips[2] give $[\alpha]_D =$

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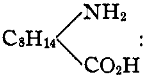
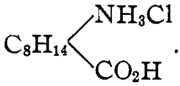
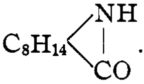
[1] *Am. Chem. J.*, **16**, 503 (1894).

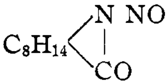
[2] *Ibid.*, **24**, 290 (1900).

53.7° for the saturated solution (about 7.5%). Subst., 0.415, 0.613; H_2O, 20.5, 21.2; depression, 0.199, 0.278; mol. wt. found, 187, 191; Calc. for  $C_8H_{14}\left\langle\begin{matrix}NH_2\\CO_2H\end{matrix}\right.$: 171.

Aminodihydrocampholytic Acid Hydrochloride,  $C_8H_{14}\left\langle\begin{matrix}NH_3Cl\\CO_2H\end{matrix}\right.$.—A few grams of the free acid were shaken with a few cc. of water and sufficient hydrochloric acid was added to give a green color to methyl violet paper. The solution was then partially evaporated and upon allowing to cool the hydrochloride separated. It was filtered and recrystallized from hot water. A melting point of 262–263° was found. Recrystallizing again gave a product melting at 261–262°, which is the same as that reported by Noyes.[1]

$[\alpha]_D^{26} = 41.3°$; 1 g. in 10 cc. of water solution.

Aminodihydrocampholytic Acid Anhydride,  $C_8H_{14}\left\langle\begin{matrix}NH\\|\\CO\end{matrix}\right.$.—This substance was prepared either by treating the free acid with acetic anhydride or by treating the hydrochloride of the acid with sodium acetate and acetic anhydride and subsequently heating the mixture with an excess of sodium hydroxide. In the latter method it is probable that the acetyl derivative is formed, as the similar liquid layer was always formed on addition of the excess of sodium hydroxide to the acetic anhydride solution. The latter method of preparation has the advantage of allowing quite impure hydrochloride to be used. The melting point, 188–189°, and the specific rotation, $[\alpha]_D^{30°} = 72.8°$, have already been published.[2]

Nitroso Derivative of Aminodihydrocampholic Acid Anhydride,  $C_8H_{14}\left\langle\begin{matrix}N\ NO\\|\\CO\end{matrix}\right.$.—Since the rotation of this substance had never been reported it was thought desirable to obtain it. It was prepared according to a method previously reported.[2]

$[\alpha]_D^{25°} = —83.3°$; 0.25 g. in 10 cc. of absolute alcohol solution.

Cyanodihydrocampholytic Acid.—Hoogewerf and Van Dorp[3] prepared this acid in just the same manner that they prepared the cyanocamphonanic acid. Rupe and Splittgerber[4] proceeded in essentially the same manner. Starting with 12.5 g. of β-camphoramidic acid and proceeding in precisely the same manner as in the preparation of the cyanocamphonanic acid, 9.5 g. of crude acid were obtained, which is an 80% yield. There was not nearly as much tendency to form a gummy pre-

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[1] *Am. Chem. J.*, 16, 504 (1894).

[2] Noyes and Potter, This Journal, 34, 1072 (1912).

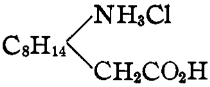
[3] *Rec. trav. chim.*, 14, 267 (1895).

[4] *Ber.*, 40, 4313 (1900).

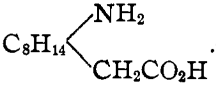
cipitate as was noted in the case of the cyanocamphonanic acid. The crude acid was purified by dissolving in 8% ammonia and precipitating with hydrochloric acid. One such procedure sufficed to bring the melting point up to 109–110°. A portion was recrystallized again in the same manner but no change in the melting point was observed. The above is the melting point observed by Hoogewerf and Van Dorp.[1]

$[\alpha]_D^{22°} = 25.3°$; 0.6 g. in 10 cc. of alcohol solution. Hoogewerf and Van Dorp give the specific rotation $[\alpha]_D = 18.12°$ for a 6% alcohol solution.

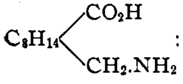
Since they purified their acid by recrystallization from hot water, in order to clear up the remote possibility of this causing the difference in the rotation, some of the crude acid was purified by their method, but a rotation taken after the fourth recrystallization, gave a value $[\alpha]_D = 25.2°$ and after the fifth recrystallization $[\alpha]_D = 25.3°$, so there is little doubt but that this is the correct value.

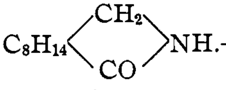
β-Aminocampholic Acid Hydrochloride,  $C_8H_{14}<\begin{matrix}NH_3Cl\\CH_2CO_2H\end{matrix}$.—Starting with cyanodihydrocampholytic acid the procedure for the preparation, separation, and purification of this substance was the same as the preparation of the α-aminocampholic acid hydrochloride. It was found, however, that the reduction in the case in hand was not as complete as with the cyanocamphonanic acid. It was found more advisable to simply separate the unchanged cyanoacid by extraction of the acid solution with ether than to use more sodium and alcohol. The β-aminocampholic acid hydrochloride is somewhat less soluble than its isomer and hence it is more easily purified. After two recrystallizations its melting point was 218–220°.

$[\alpha]_D^{26°} = 41.3°$; 0.5 g. in 10 cc. of water solution.

β-Aminocampholic Acid,  $C_8H_{14}<\begin{matrix}NH_2\\CH_2CO_2H\end{matrix}$.—About 5 g. of the pure hydrochloride were dissolved in the minimum amount of water and sufficient strong sodium hydroxide solution (3 cc. = 1 g.) was added to give a solution neutral to phenolphthalein. The free acid, which was precipitated, was filtered, dissolved in hot water, partially evaporated and filtered. This was repeated until a substance free from chlorine was obtained, three recrystallizations in all being required.

$[\alpha]_D^{25°} = 16.4°$; 0.25 g. in 10 cc. of solution.

Subst., 0.318, 0.389; H_2O, 22.1, 21.8; depression, mol. wt. found, 199, 197. Calc. for  $C_8H_{14}<\begin{matrix}CO_2H\\CH_2.NH_2\end{matrix}$: 185.

β-Camphidone,  $C_8H_{14}<\begin{matrix}CH_2\\CO\end{matrix}>NH$.—This compound was prepared from

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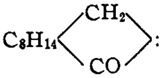
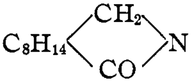
[1] *Rec. trav. chim.*, 14, 267 (1895).

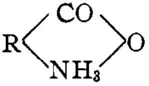
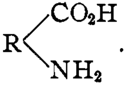
the β-aminocampholic acid hydrochloride in just the same manner as the α-camphidone was prepared from the α-aminocampholic acid. A melting point of 234–235° was found and a specific rotation $[\alpha]_D^{24°} = 63.2°$; 0.25 g. in 5 cc. of alcohol solution. Rupe and Splittgerber[1] report a melting point of 225° and its specific rotation $[\alpha]_D = 66.5°$ for a 10% solution in benzene. An analysis of the compound was made.

Calc. for  $C_8H_{14}\left\langle\begin{matrix}CH_2\\CO\end{matrix}\right\rangle:N$ = 8.38; found: N = 8.37.

Nitroso Derivative of β-Camphidone,  $C_8H_{14}\left\langle\begin{matrix}CH_2\\CO\end{matrix}\right\rangle N\,NO$.—The β-camphidone was dissolved in dilute hydrochloric acid (1 : 4) and a sodium nitrite solution was added. The yellow precipitate was filtered and recrystallized from alcohol two times, when a melting point of 164–165° is given. A portion recrystallized a third time showed the same melting point.

$[\alpha]_D^{23°} = 103°$; 0.25 g. in 10 cc. of solution.

Summary.

It is shown in this paper that the specific rotations of some amino derivatives of camphoric acid are consistent with the view that those amino acids which can form cyclic salts containing quinquivalent nitrogen and a ring of six atoms form salts having the general formula  $R\left\langle\begin{matrix}CO\\NH_3\end{matrix}\right\rangle O$ in aqueous solutions. Amino acids which would give a ring of seven atoms in forming a cyclic salt appear to exist in solution as compounds of the form,  $R\left\langle\begin{matrix}CO_2H\\NH_2\end{matrix}\right.$. These relations furnish strong evidence that nitrogen is in reality quinquivalent in ammonium salts and that the hydrogen of the acid combines with the nitrogen instead of remaining combined with the acid radical, as Werner has supposed.

Several new compounds have been prepared and the specific rotations of a number of known compounds have been determined.

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ON THE PRESENCE OF HISTIDINE-LIKE SUBSTANCES IN THE PITUITARY GLAND (POSTERIOR LOBE).

BY T. B. ALDRICH.

Received November 5, 1914.

In 1896, A. Kossel discovered among the cleavage products of sturine

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[1] *Ber.*, 40, 4313 (1907).