

sium chloride in the absence of solvents. General applications and conclusions from this sealed-tube method of preparation have been discussed.

AMES, IOWA

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

OPTICALLY ACTIVE SALTS OF 2-NITRO-OCTANE

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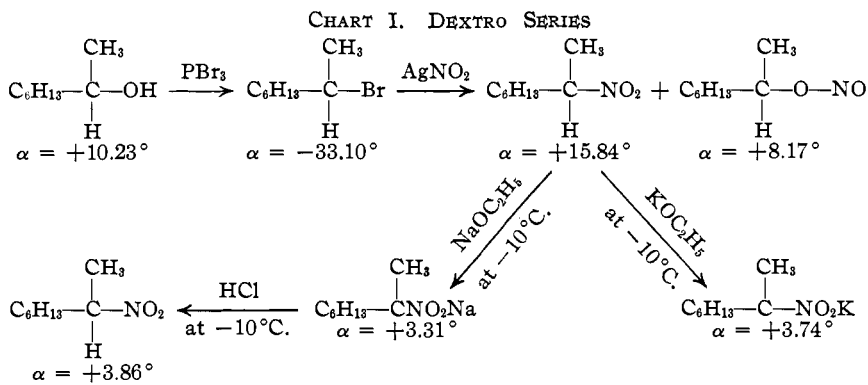
In connection with the general theory of tautomerism the conversion of an optically active secondary nitro compound into salts of the aci-form which are also optically active is of considerable theoretical importance. Only one example is recorded in the literature at the present time, namely, Kuhn's studies on 2-nitrobutane.¹ Since this work represents the only experimental evidence against the classical formulas for the aci-form, it was thought that the preparation and further study of another secondary nitro compound would furnish confirmatory evidence and additional knowledge concerning the tautomerism of these types of compounds.

The following schematic diagram shows the preparation of the optically active 2-nitro-octanes and indicates the products obtained from them. It also lists the optical rotations of all the compounds and summarizes the results obtained during this investigation.

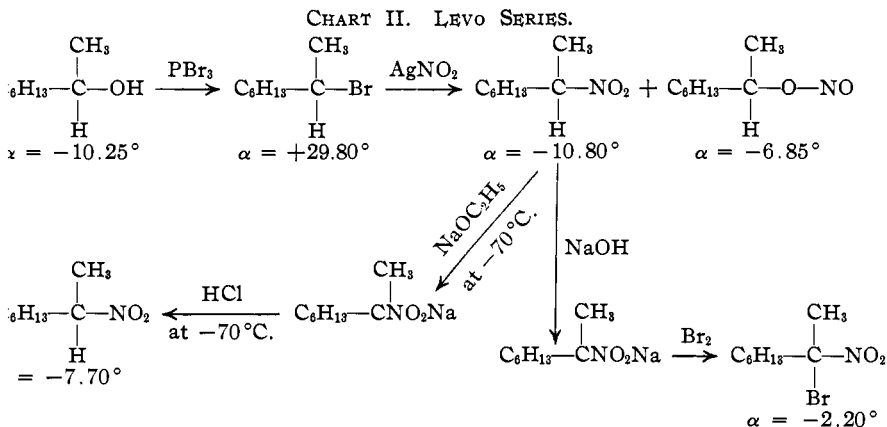
The dextro series represents the purer compounds. It is evident that a slight racemization took place during the preparation of the *l*-bromide from the *l*-octanol-2.

The above data fully confirm Kuhn and Albrecht's observation that the sodium salts of optically active secondary nitro compounds are also optically active. That this optical activity is actually due to the sodium salts was proved as follows.

(1) The optical rotation of equivalent amounts of the nitro compound



¹ Kuhn and Albrecht, *Ber.*, **60**, 1297 (1927).



and sodium ethylate reached a constant value as soon as the solutions were mixed. The reading remains constant over a period of twenty-four hours.

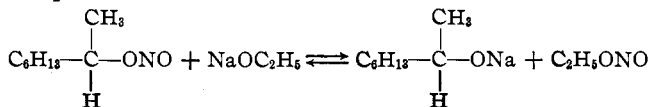
(2) The use of two equivalents of sodium ethylate gives exactly the same rotation as one equivalent. This shows that conversion to the salt is complete and that the observed activity is not due to unreacted nitro compound.

(3) The nitro compound can be regenerated from the sodium salt. The product so obtained has a lower rotation than the original nitro compound, 24% in case of the dextro, where the reconversion was carried out at -10° , and 71% in case of the levo, where the reconversion was carried out at -70° . The fact that the regenerated nitro compound was active at all shows that the sodium salt was active.

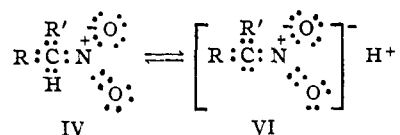
(4) The use of one and two equivalents of potassium ethylate gave optically active potassium salts whose rotations were the same (within experimental error) as those of the sodium salts. This shows that the metal used has no particular effect on the rotation of the aci-nitro form and hence the optical activity is due to the negative aci-ion.

(5) Treatment of the (*l*) sodium salt with bromine gave (*l*)-2-bromo-2-nitro-octane which was also optically active.

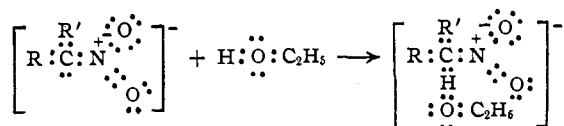
(6) The (*d*) octyl-2-nitrite which possessed a lower rotation than that of the nitro compound was also treated with sodium ethylate. The rotation observed as soon as possible was $+3.46^\circ$, but on standing the rotation slowly *increased* to $+6.00^\circ$. With two equivalents of sodium ethylate the rotation changed in the same manner except that a shorter time was necessary to reach the equilibrium value. This change in rotation was due to the saponification of the nitrite



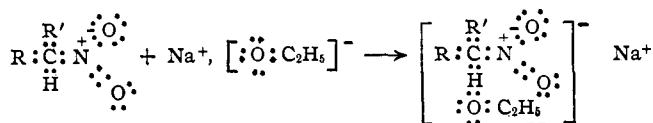
fact that the rotations of the salts were remarkably constant over a period of *twenty-four hours* would seem to discount the racemization theory and favor the idea that there exist two forms of the aci-nitro ion, (V) and (VI). This is in agreement with the work of Branch and Deelman,⁹ who studied the change in conductivity which took place on the addition of hydrochloric acid to the sodium salt of the aci-nitro compound. An abnormal conductance drop took place at the start followed by a slow gradual drop for the conversion of the greater part of the aci-nitro salt back to the normal nitro form. Branch and Deelman suggest Form (III) for that portion which caused the rapid initial drop. Whether Form (III) or (VI) is correct cannot be stated at the present time, but the experimental data on both conductivity and optical activity can be correlated by postulating the presence of two different forms of the negative ion. The chief objection to such an assumption is the fact that racemization of VI does not occur readily, which means that the ions V and VI are not in rapid equilibrium with each other. While at first this may seem unlikely, it is not impossible if the following mechanism for ion formation is considered. (1) Partial ionization of the nitro form to give the asymmetric ion VI



This ion is probably stabilized by solvation

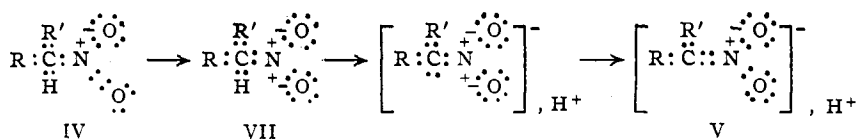


or, the same solvated ion may be produced by the direct combination of the nitro compound with the ethylate ion:



The temperature effect discussed above is good evidence in favor of stabilization of this asymmetric ion by combination with the solvent since solvation is known to be dependent on the temperature. This combination of VI with a molecule of alcohol prevents its conversion to the inactive ion V. (2) Primary rearrangement followed by ionization to give the inactive ion V.

⁹ Branch and Deelman, *THIS JOURNAL*, **49**, 1765 (1927).



This rearrangement of IV to VII parallels the conversion of a ketone into its active form, *i. e.*, changing the non-polar oxygen into a semi-polar oxygen atom.¹⁰

From an electronic point of view, Form (V) should be formed in preference to Form (VI), since it represents a more stable arrangement and electron distribution. This agrees with the experimental facts that only a small part of the salt is active and only a portion of the regenerated nitro compound is active.

Experimental

Preparation of *d*- and *l*-Octanol-2.—Octanol-2 was resolved by crystallization of the brucine salts of the phthalic acid ester according to the procedure given in "Organic Syntheses."¹¹ The *d*-octanol-2 distilled at 86° at 20 mm.; $\alpha_D^{25} +10.23^\circ$; and *l*-octanol-2 at 84° at 16 mm.; $\alpha_D^{25} -10.25^\circ$.

***l*-2-Bromo-octane.**—In a 500-cc. three-necked flask fitted with a stirrer, a thermometer reaching to the bottom of the flask and a separatory funnel, was placed 39 g. of *d*-octanol-2. The alcohol was cooled to -5° by means of an ice-salt bath and 90 g. of phosphorus tribromide was added drop by drop so that the temperature did not rise above $+5^\circ$. The mixture was allowed to stand overnight and slowly come to room temperature. It was then heated on a boiling water-bath for one hour and cooled. The mixture was decomposed with 200 cc. of ice water and the bromide taken up in ether. The ether solution was dried and the ether distilled. The residual oil was vacuum distilled; 47 g. of *l*-2-bromo-octane boiling at 83–84° at 18 mm. was obtained; $\alpha_D^{25} -33.1^\circ$; n_D^{20} 1.4500; yield, 80%.

***d*-2-Bromo-octane.**—This isomer was obtained by exactly the same procedure; 49 g. of *l*-octanol-2 yielded 62 g. of *d*-2-bromo-octane; b. p. 83–84° at 18 mm.; $\alpha_D^{25} +29.8$; n_D^{20} 1.4501; yield, 85.3%.

***d*-2-Nitro-octane.**—Eighty cc. of dry benzene and 60 g. of finely powdered silver nitrite were placed in a 200-cc. three-necked flask fitted with a stirrer, reflux condenser and dropping funnel. The mixture was cooled to 0° and 47 g. of *l*-2-bromo-octane run in slowly with stirring. The reaction mixture was stirred for three hours at 0° and then heated on a water-bath for six hours. The benzene solution was decanted and the residue washed with two 25-cc. portions of benzene. The benzene was distilled and the mixture of 2-octyl nitrite and 2-nitro-octane was carefully fractionated *in vacuo* by the use of a modified Claisen fractionating flask. After three fractionations 5.5 g. of *d*-2-nitro-octane was obtained as a light yellow oil; b. p. 102–105 at 23 mm.; yield, 14.4%; d_4^{20} 0.9224; n_D^{20} 1.4324; M_D (calcd.), 45.65; M_D (found), 44.75; $\alpha_D^{25} +15.84$ (abs. ethyl alcohol).

Anal. Subs., 0.1042: CO₂, 0.2308; H₂O, 0.0996. Calcd. for C₈H₁₇NO₂: C, 60.37; H, 10.69. Found: C, 60.41; H, 10.62.

¹⁰ Carothers, THIS JOURNAL, 46, 2229 (1924); Shriner, Struck and Jorison, *ibid.*, 52, 2064 (1930).

¹¹ "Organic Syntheses," J. Wiley and Sons, Inc., New York, 1926, Vol. VI, p. 68.

The *d*-2-octyl nitrite obtained was also a light yellow oil distilling at 86–90° at 18 mm.; yield, 9.8 g. or 25.6%; d_{20}^{20} 0.852; n_D^{20} 1.4279; M_D (calcd.), 45.25; M_D (found), 47.7; α_D^{25} +8.17° (abs. alcohol).

***l*-2-Nitro-octane.**—The isomer was obtained by the same procedure as above; 60 g. of *d*-2-bromo-octane and 60 g. of silver nitrite yielded 7.4 g. of *l*-2-nitro-octane; yield, 15.0%; b. p. 100–103° at 18 mm.; d_{20}^{20} 0.9165; n_D^{20} 1.4292; M_D (calcd.), 45.65; M_D (found) 44.65; α_D^{25} – 10.8° (abs. alcohol).

The *l*-2-octyl nitrite was obtained in 24.1% yield; b. p. 85–90° at 18 mm.; d_{20}^{20} 0.857; n_D^{20} 1.4218; M_D (calcd.), 45.25; M_D (found), 46.8; α_D^{25} – 6.85° (abs. alcohol).

Sodium Salt of *d*-2-Nitro-octane.—A standard solution of sodium ethylate in absolute ethyl alcohol was prepared by dissolving metallic sodium in absolute alcohol. A sample of 0.2840 g. of *d*-2-nitro-octane was mixed with 4.44 cc. of 0.416 *N* sodium ethylate solution (1 equivalent) and then diluted to 20 cc. The rotation was observed immediately and at one-hour intervals over a period of twenty-four hours, during which time the readings were constant within the experimental error of reading. All rotations were made with D sodium light and at 25°; average, α_D^{25} +3.31°.

A second solution was prepared using 0.3016 g. of *d*-2-nitro-octane and 9.10 cc. of 0.416 *N* (2 equivalents) sodium ethylate solution. The readings were again constant over a period of twelve hours; average, α_D^{25} +3.29°.

Potassium Salt of *d*-2-Nitro-octane.—Equivalent quantities of a standard solution of potassium ethylate in absolute alcohol and *d*-2-nitro-octane were mixed and the rotation was observed over a period of twenty-four hours. The readings were constant; average, α_D^{25} +3.74°.

With two equivalents of potassium ethylate the optical activity of the solution also remained constant over a period of 23 hours; average, α_D^{25} +3.96°.

Preparation of *l*-2-Bromo-2-nitro-octane.—(a) To 1.0 g. of *l*-2-nitro octane was added 25 cc. of 0.3286 *N* sodium ethylate. Aqueous bromine was added until the solution became permanently yellow. The reaction flask was cooled in a freezing mixture. The solution was allowed to stand for five minutes, after which enough sodium thio-sulfate was added to remove the color of the bromine; 25 cc. of water was added and then 100 cc. of ether to extract the product. The ether solution was dried and the ether evaporated at room temperature by use of suction. The air stream was purified by use of an askarite–dehydrite tube; 0.3087 g. of the residue of *l*-2-bromo-2-nitro-octane was tested for rotation; α_D^{25} – 2.92°.

(b) A second sample of 2 g. of *l*-2-nitro-octane was treated with an excess of dilute aqueous sodium hydroxide. The aqueous solution was washed once with ether to take out any unreacted *l*-2-nitro-octane. The aqueous layer was separated and treated with an excess of bromine. The *l*-2-bromo-2-nitro-octane obtained had a very irritating odor; α_D^{25} – 2.22°; n_D^{20} 1.4499; d_{20}^{20} 1.113; M_D (calcd.), 54.5; M_D (found), 57.4.

Anal. Subs., 0.3376: 15.37 cc. of 0.0935 *N* AgNO₃. Calcd. for C₈H₁₆BrNO₂: Br, 33.60. Found: Br, 34.05.

Reaction of *d*-2-Octyl Nitrite with Sodium Ethylate.—A sample of 0.3103 g. of *d*-2-octyl nitrite was treated with an equal molal quantity of sodium ethylate (2.63 cc. of 0.740 *N*). Readings were made over a period of one hundred hours. The readings changed from an initial value of α_D^{25} +3.46° to a maximum of α_D^{25} +6.00°. Longer standing caused the rotation to drop slightly. A sample of 0.3215 g. of *d*-2-octyl nitrite was treated with two equivalents of 0.740 *N* sodium ethylate. The average of ten readings over an eighty-hour period gave α_D^{25} +6.15°. The initial reading was α_D^{25} +5.71°.

Conversion of the Sodium Salt of *d*-2-Nitro-octane Back to *d*-2-Nitro-octane by an Addition of Acid at –10°.—(a) A 0.4575-g. sample of *d*-2-nitro-octane was made up to 20 cc. volume by adding 95% alcohol. The rotation was taken and found to be α_D^{25}

+12.35° instead of +15.84° (abs. alcohol). The solution was then treated with 2.33 cc. of 1.233 *N* sodium ethylate at -10°. An excess of alcoholic hydrogen chloride (6.5 cc. of 0.616 *N*) was then added and just enough water (2 cc.) to dissolve the sodium chloride formed in the reaction. The solution was diluted to 40 cc. with 95% alcohol and 20 cc. (0.2289 g. of *d*-2-nitro-octane) used for taking a rotation. Readings were made over a period of eighteen hours; average, $\alpha_D^{25} +3.86^\circ$. This is 24.12% of the rotation of the unreacted *d*-2-nitro-octane.

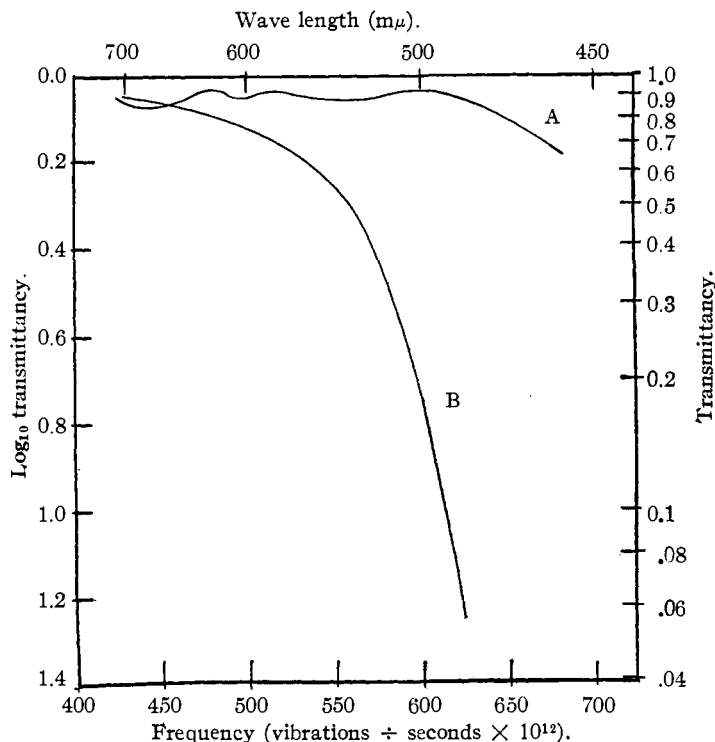


Plate I.—Absorption spectra of *d*-2-nitro-octane and its sodium salt.

(b) To remove the effect of the water on the rotation, the other 20-cc. portion after the addition of the acid was diluted with water and the *d*-2-nitro-octane extracted with 25 cc. of ether. The ether solution was dried with anhydrous magnesium sulfate. The ether was distilled off and the residue dissolved in absolute alcohol. This gave $\alpha_D^{25} +2.86^\circ$. Part of the nitro compound was probably lost due to slight solubility in the alcohol-water layer.

Conversion of the Sodium Salt of *l*-2-Nitro-octane Back to *l*-2-Nitro-octane at Temperature of Carbon Dioxide Snow (-70°).—To 0.5 g. of *l*-2-nitro-octane was added an excess (10 cc. of 0.3286 *N*) of sodium ethylate. The solution was cooled by carbon dioxide snow and an excess of alcoholic hydrogen chloride added. The reaction mixture was allowed to stand for ten minutes in carbon dioxide snow. Water was added and the *l*-2-nitro-octane extracted with ether. A 0.3462-g. sample of the recovered 2-nitro-octane was made up to 20 cc. volume with absolute alcohol and the rotation taken: $\alpha_D^{25} -7.7^\circ$, or 71.2% of the unreacted *l*-2-nitro-octane.

Absorption Spectra of *d*-2-Nitro-octane and the Sodium Salt of *d*-2-Nitro-octane.—The absorption spectra (Plate I) were determined in a K and E color analyzer which permitted measurements in the visible range only. A solution of 0.5191 g. of *d*-2-nitro-octane in 20 cc. of absolute alcohol was used for obtaining curve (A) and a sample of 0.5041 g. of 2-nitro-octane which was treated with one equivalent of sodium ethylate solution and diluted to 20 cc. was used to obtain curve (B).

Summary

1. The preparation of (*d*) and (*l*) 2-nitro-octanes is described.
2. The sodium and potassium salts of *d*-2-nitro-octane were found to be optically active to the same extent.
3. The *d*-2-nitro-octane regenerated from the sodium salt at -10° was optically active to the extent of 24.12% of the original *d*-2-nitro-octane.
4. By use of very low temperature for the reaction, the regenerated *l*-2-nitro-octane was optically active to the extent of 71.2% of the original *l*-2-nitro-octane.
5. Optically active *d*-2-bromo-2-nitro-octane was prepared from the active sodium salt of *d*-2-nitro-octane.

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[CONTRIBUTION FROM THE ZOOLOGY DEPARTMENT, UNIVERSITY OF WISCONSIN]

THE RELAXATIVE HORMONE OF THE CORPUS LUTEUM. ITS PURIFICATION AND CONCENTRATION¹

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It is a matter of common knowledge, at least among those versed in the physiology of reproduction, that the pelvis of several species of mammals is modified during pregnancy to facilitate the birth of young. These pelvic modifications commonly involve the ligaments of the symphysis pubis and ilio-sacral unions in a fashion which enables these bones to move apart and thus increase the diameter of the pelvic canal. In some animals, only the ilio-sacral unions are changed, while in others both these and the symphysis pubis are affected. One of the most striking examples of this phenomenon is found in pregnant guinea pigs. The pelvic ligaments of these animals begin to show signs of loosening, both at the ilio-sacral and pubic regions, about the middle of pregnancy and they become more and more pronounced with the approach of parturition. At the termination of pregnancy the ilia can be freely moved, and a finger can be placed between the pubic bones at the symphysis. This remarkable modification of the guinea pig pelvis has, for lack of a better term, been designated as ligamentus relaxation.

¹ This work has been assisted by grants from the committee for Research on Problems of Sex of the National Research Council.