3. The moments obtained by direct measurement are much smaller than has been calculated from solubility data. While dipole forces undoubtedly play a part in determining solubility, apparently not enough is known about them to permit an even semi-quantitative calculation of electric moments by this method.

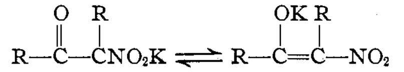
NOTRE DAME, INDIANA RECEIVED SEPTEMBER 10, 1935

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

Asymmetric Syntheses. IV. The Action of Optically Active Nitrates on 2-Bromofluorene

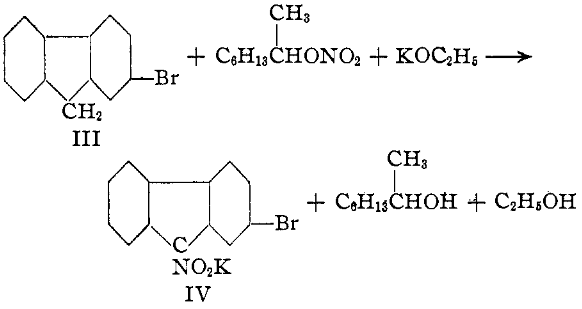
BY J. T. THURSTON AND R. L. SHRINER

The reaction between optically active nitrates and cyclic ketones[1] led to the formation of salts which could possess either structure[2] I or II. In order to avoid this, a study has been made of the action of optically active nitrates on an active methylene compound which cannot undergo such tautomerization.



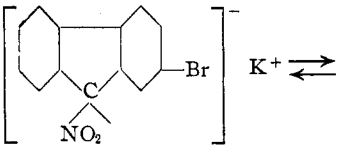
$$\underset{\text{I}}{R-\overset{\overset{O}{\|}}{C}-\overset{\overset{R}{|}}{C}NO_2K} \rightleftharpoons \underset{\text{II}}{R-\overset{\overset{OK}{|}}{C}=\overset{\overset{R}{|}}{C}-NO_2}$$

Since Wislicenus and Waldmüller[3] showed that fluorene would react with ethyl nitrate in the presence of potassium ethoxide to give the potassium salt of 9-nitrofluorene, it was decided to study the reaction between the optically active 2-octyl nitrates and 2-bromofluorene (III).

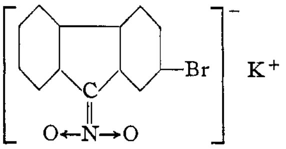


The latter compound (III) contains an active methylene group but cannot undergo enolization. The presence of the bromine in one ring renders the molecule unsymmetrical so that carbon atom 9 in the product (IV) may be asymmetric.

Treatment of 2-bromofluorene with *d*-2-octyl nitrate in the presence of potassium ethoxide yielded the potassium salt of 9-nitro-2-bromofluorene which possessed a very slight optical activity. Two independent preparations gave specific rotations[4] of +4.48 and +4.33°. The observed rotations were very low, +0.06 ± 0.01° and +0.05 ± 0.01°, but the absolute alcohol solutions of the salts were distinctly optically active. The *l*-2-octyl nitrate gave a very low specific rotation of −1.71°. The salts racemized readily. The activity of these salts indicates that at least a partial asymmetric synthesis was achieved by the optically active reagents. At least part of the salt must exist as the asymmetric ion (V) since the other form of the ion (VI) is not asymmetric.

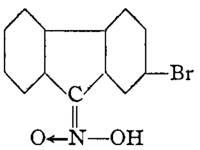


V

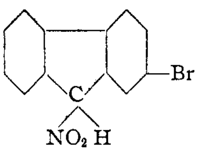


VI

Immediate treatment of the *d*-potassium salt with acid gave the *aci*-9-nitro-2-bromofluorene (VII) which was optically inactive. This *aci*-form (VII) was a solid, m. p. 132°. It was readily soluble in sodium carbonate solution, and gave a green color with ferric chloride. This *aci*-form was transformed into the *normal*-nitro compound (VIII) by heating it in alcoholic solution. The *normal*-nitro compound (VIII) gave



VII



VIII

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[1] Shriner and Parker, THIS JOURNAL, **55**, 766 (1933).

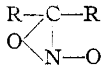
[2] Horne and Shriner, *ibid.*, **55**, 4652 (1933).

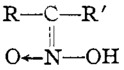
[3] Wislicenus and Waldmüller, *Ber.*, **41**, 3334 (1908).

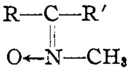
[4] All specific rotations reported in this paper were determined at 25° with sodium D light.

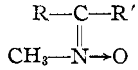
no color with ferric chloride, and was insoluble in sodium carbonate solution. These two compounds, therefore, constitute another case in which both the *aci*- and *normal*-forms have been isolated. It is worth pointing out that there should be two geometric isomers of the *aci*-form (VII); one, in which the hydroxyl is *syn* to the bromine in the ring, and a second in which the hydroxyl is *anti* to the bromine. Only one form of VII was obtained in the present work.

Air oxidizes these potassium salts to 2-bromofluorenone and potassium nitrite, a reaction which has been observed previously by Wislicenus and Waldmüller in the case of the salts of 9-nitrofluorene.[3] Bromine converted the *d*-potassium salt into 9-nitro-2,9-dibromofluorene, which was optically inactive. A quantitative bromine titration of the potassium salt, according to the general procedure of Meyer and Wertheimer,[5] showed that 90% of the theoretical amount of bromine was taken up. Titration of the *aci*-form VII gave a 50% absorption of bromine, whereas the *normal*-nitro form VIII did not absorb bromine at all under the conditions of the titration. The fact that the *aci*-form changes over to the *normal*-form probably accounts for the bromine titration value of 50%. These results are of importance since they constitute some evidence against the cyclic structure, IX, which was originally proposed for the *aci*-form by Holleman,[6] and Hantzsch and Schultze.[7] The ready formation of the bromonitro compound from the salt and the absorption of bromine by the *aci*-form are best explained by the structure X for the *aci*-modification rather than by IX. These *aci*-forms parallel the nitrogen alkylated ketoximes which have been shown[8] to possess the structures XI and XII. As mentioned above, none of the *syn* and *anti* forms of *aci*-nitro compounds have been obtained as yet.

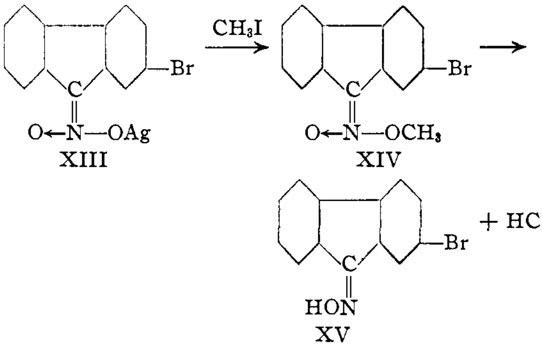

IX


$R-\underset{\underset{O\leftarrow N-OH}{\|}}{C}-R'$
X


$R-\underset{\underset{O\leftarrow N-CH_3}{\|}}{C}-R'$
XI


$R-\underset{\underset{CH_3-N\rightarrow O}{\|}}{C}-R'$
XII

Nenitzescu and Isacescu[9] have found that alkylation of sodium or potassium salts of nitro compounds leads to degradation products which may be best explained by an intermediate nitronic ester. In the present study it was found possible to obtain the methyl nitronic ester (XIV) by treating the silver salt of 9-nitro-2-bromofluorene (XIII) with methyl iodide.



This nitronic ester (XIV) was very unstable, and readily decomposed into 2-bromofluorenone oxime (XV) and formaldehyde. This decomposition is characteristic of nitronic esters[10] and shows that alkylation occurred on the oxygen atom, and not on the carbon atom.

Experimental

2-Bromofluorene.—To 125 g. of fluorene and about 1 g. of iodine, dissolved in 350 cc. of boiling benzene, was added during the course of three hours 120 g. of dry bromine dissolved in 200 cc. of cold benzene. This solution was refluxed for another hour, cooled, washed with water and finally with sodium bisulfite solution. After distilling the benzene and water, the product was fractionated twice. About 20 g. of unchanged fluorene, 75 g. of product boiling at 157–162° (1–2 mm.) and 40–50 g. of undistillable tar were obtained. The crude product was recrystallized from three 500-cc. portions of alcohol, and melted sharply[11] at 113°. The yield was 65 g., or 35% of the theoretical.

Anal. Calcd. for $C_{13}H_9Br$: Br, 32.65. Found: Br, 32.66.

***dl*-, *d*- and *l*-2-Octyl Nitrates.**—These were prepared according to the method previously described.[1] *dl*-2-Octyl nitrate boiled at 92–94° (17 mm.); n^{20}_D 1.4240. *d*-2-Octyl nitrate boiled at 96–97° (16 mm.; $[\alpha]^{25}_D$ +16.00°; n^{20}_D 1.4270. *l*-2-Octyl nitrate boiled at 95–97° (20 mm.); $[\alpha]^{25}_D$ −15.28°; n^{25}_D 1.4292.

Condensation of 2-Bromofluorene with *dl*-2-Octyl Nitrate.—A solution of 5.6 g. of *dl*-2-octyl nitrate and 6 g. of 2-bromofluorene in 80 cc. of absolute ether was added to a solution of potassium ethoxide prepared from 1 g. of potassium, 7 cc. of absolute ethyl alcohol and 25 cc. of absolute ether. The reaction mixture was maintained at 45° by means of a water-bath; after about two hours half of the ether was distilled. The remaining solution was filtered and poured into 200 cc. of low-boiling petroleum ether. The yellow, precipitated potassium nitro salt was purified by dissolving in a very small amount of ethyl

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(5) Meyer and Wertheimer, *Ber.*, **47**, 2374 (1914).

(6) Holleman, *Rec. trav. chim.*, **13**, 405 (1894); **14**, 129 (1895).

(7) Hantzsch and Schultze, *Ber.*, **29**, 699, 2251 (1896).

(8) Brady and Mehta, *J. Chem. Soc.*, **125**, 229 (1924); Sutton and Taylor, *ibid.*, 219 (1931).

(9) Nenitzescu and Isacescu, *Ber.*, **63**, 2484 (1930).

(10) Wislicenus and Waldmüller, *ibid.*, **41**, 3334 (1908); Arndt and Rose, *J. Chem. Soc.*, 1 (1935).

(11) Courtot, *Ann. chim.*, [10] **14**, 56 (1930).

acetate and reprecipitated with equal parts of benzene and petroleum ether. The product, which gave a green color with a drop of ferric chloride, was obtained in yields of 62.5% of the theoretical.

Anal. Calcd. for $C_{13}H_7O_2NBrK$: K, 11.89; Br, 24.36; N, 4.27. Found: K, 12.11; Br, 24.50; N, 4.05.

Condensation of 2-Bromofluorene with *d*-2-Octyl Nitrate.—The same general procedure as above was followed, using *d*-2-octyl nitrate. However, the temperature was maintained at 35°, and the ether was removed at diminished pressure. The yield of the crude salt, giving an immediate specific rotation[4] in absolute alcohol of +4.33°, was 1.5 g. Another sample of the salt, prepared in the same manner, gave an immediate specific rotation in absolute alcohol of +4.48°. Below 30° the reaction did not take place, and between 30 and 35° the yields were very small. The order of addition or molar ratio of the reactants had no effect on the yield or optical activity of the salt.

Anal. Calcd. for $C_{13}H_7O_2NBrK$: K, 11.89. Found: K, 11.51.

Condensation of 2-Bromofluorene with *l*-2-Octyl Nitrate.—Exactly the same procedure as above was followed using *l*-2-octyl nitrate, and the specific rotation[4] of the salt in absolute alcohol was immediately determined and found to be −1.71°.

Reaction between *dl*-2-Octyl Nitrate and Potassium Ethoxide.—A control experiment identical with the above procedure except that the 2-bromofluorene was omitted showed that the potassium 2-octoxide was soluble in the concentrations of alcohol, ether and petroleum ether used in the above reactions, and, therefore, could not contaminate the salts of the nitro compounds.

2-Bromofluorenone from the Potassium Nitro Salt.—The potassium nitro salt in alcohol solution on exposure to air for several days was oxidized to potassium nitrite and 2-bromofluorenone melting at 146°. The latter yielded an oxime which melted at 196°, while the recorded[12] melting point is 194–195°.

Anal. Calcd. for $C_{13}H_7OBr$: Br, 30.88. Found: Br, 31.49.

Aci-9-Nitro-3-bromofluorene.—The bright yellow precipitate, obtained by the action of dilute acetic acid upon an aqueous solution of the *dl*-potassium nitro salt, after recrystallization from hot alcohol, melted at 132°. It was soluble in dilute alkalies and gave a green color with a drop of ferric chloride. The optically active salts gave the same optically inactive *aci*-form.

Anal. Calcd. for $C_{13}H_8O_2NBr$: N, 4.83; Br, 27.55. Found: N, 5.01; Br, 27.78.

9-Nitro-2-bromofluorene.—When an alcoholic solution of the *aci*-nitro form was boiled it was converted into the normal nitro form which crystallized when the solution cooled. The colorless plates, after recrystallization from ethyl acetate, melted at 170°, were insoluble in dilute alkalies and did not give a color with a drop of ferric chloride. On longer standing, the original filtrate deposited crystals of 2-bromofluorenone, melting at 146°.

Anal. Calcd. for $C_{13}H_8O_2NBr$: N, 4.83; Br, 27.55. Found: N, 4.84; Br, 27.59.

2,9-Dibromo-9-nitrofluorene.—An alcoholic solution of the *dl*-potassium nitro salt on treatment with a solution of bromine in absolute alcohol gave the dibromo compound, which was precipitated by the addition of water. After recrystallization from an alcohol–ethyl acetate mixture, the yellow needles melted at 139°.

Anal. Calcd. for $C_{13}H_7O_2NBr_2$: Br, 43.32; N, 3.79. Found: Br, 43.38; N, 4.03.

The *d*-potassium nitro salt, by exactly the same procedure as above, gave the same dibromo compound, which was washed with a small amount of alcohol, dried in a vacuum desiccator and the optical rotation immediately taken. It was optically inactive.

Methylation of the Silver Salt.—The silver salt was prepared in almost quantitative yields by the addition of silver nitrate solution to an aqueous solution of the potassium salt. To 2 g. of the dried silver salt suspended in 5 cc. of ether cooled to −10° was added 3 cc. of methyl iodide dissolved in 6 cc. of ether. After shaking the suspension for six hours, the mixture was filtered and the filtrate evaporated at diminished pressure. After four recrystallizations from a mixture of ether and petroleum ether the product still melted over a wide range, 72–80°. When stored in a desiccator the odor of formaldehyde was noted in a short time. The analysis for nitrogen was high indicating the presence of some of its decomposition product, 2-bromofluorenone oxime.

Anal. Calcd. for $C_{14}H_{10}O_2NBr$: N, 4.60. Found: N, 4.96.

When the above nitronic ester was dissolved in alcohol and warmed for about thirty minutes, the transformation into the oxime was complete. The 2-bromofluorenone oxime melted at 195° and a mixed melting point with an independently prepared specimen showed no depression.

Bromine Titrations.—The general procedure of Meyer and Wertheimer was followed, using a weighed amount of the *dl*-potassium nitro salt, which was dissolved in cold alcohol and quickly titrated with a freshly prepared methyl alcohol solution of bromine. The excess bromine was removed by adding 2–3 cc. of 10% β-naphthol solution. After excess 20% potassium iodide solution was added and warmed for twenty minutes, the liberated iodine was titrated with 0.1 *N* thiosulfate solution using starch as an outside indicator.

Compound	Bromine absorption % of calcd.
dl-Potassium salt	89.2–90.4
Aci-nitro form	50.4
Normal nitro form	0.0
Nitronic ester	48.8–53.5
2-Bromofluorenone oxime	50.76

Since the nitronic ester breaks down into the oxime, the values for these two compounds are similar.

Summary

The condensation of 2-bromofluorene with *d*- or *l*-2-octyl nitrate produced the potassium salts of 9-nitro-2-bromofluorene. These salts were slightly optically active.

Acidification of the salts gave optically inactive

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[12] Courtot, *Ann. chim.*, [10] **14**, 62 (1933).

aci-9-nitro-2-bromofluorene. Treatment with bromine gave 9-nitro-2,9-dibromofluorene which was also optically inactive.

Methylation of the silver salt of 9-nitro-2-bromofluorene gave an unstable nitronic ester which readily decomposed into 2-bromofluorenone oxime and formaldehyde.

The *aci*-nitro form of 9-nitro-2-bromofluorene readily rearranged to the *normal* form. The latter did not absorb bromine whereas the *aci*-form absorbed 50% of the theoretical amount.

URBANA, ILLINOIS RECEIVED AUGUST 2, 1935

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Some Derivatives of *p*-Fluorophenyl Sulfinic Acid[1]

BY RAYMOND M. HANN

In connection with a study of the action of certain sulfur compounds as possible chemotherapeutic agents in the treatment of pneumonia, a series of derivatives of *p*-fluorophenyl sulfinic acid has been prepared. The sodium salt of *p*-fluorophenyl sulfinic acid was readily obtained from fluorobenzene by the synthesis of Knoevenagel and Kenner[2] and proved to be a suitable material for the introduction of various substituents in the sulfinic acid group. Such compounds as were applicable in regard to solubility and toxicity were tested upon pneumococcus infections in mice by Dr. Sanford Rosenthal, of the Division of Pharmacology, National Institute of Health, but proved to be without therapeutic effect.

Experimental

Sodium *p*-Fluorophenyl Sulfinate Dihydrate.—Dry hydrochloric acid gas was bubbled through an ice-cold suspension of 15 g. of anhydrous aluminum chloride in a solution of 10 g. of fluorobenzene in 25 cc. of carbon disulfide until it was saturated. Dry sulfur dioxide was then introduced in a slow steady stream until the crystalline aluminum chloride was completely changed to a heavy green oily layer (three hours), which became crystalline on standing overnight at room temperature. The reaction mixture was decomposed with 200 cc. of ice water, 20% sodium hydroxide added to strong alkalinity (about 70 cc.), the suspension digested for an hour on the steam-bath, filtered, the soluble aluminum precipitated by passing in carbon dioxide, and, following a second filtration, the mother liquor concentrated to a volume of 50 cc. when a first crop of 12.7 g. of pure salt separated. A second crop, upon further concentration, brought the total yield to 17.0 g. (75% based on dihydrate). Recrystallized from one part of hot water it separated in glistening diamond shaped crystals of the dihydrate.

Anal. Calcd. for $C_6H_4O_2SNaF \cdot 2H_2O$: Na, 10.5; H_2O, 16.5. Found: Na, 10.4; H_2O, 16.7.

Benzyl-ψ-thiourea Salt of *p*-Fluorophenyl Sulfinic Acid.—Cold solutions of 1 g. of benzyl-ψ-thiourea hydrochloride in 10 cc. of 0.25 *N* hydrochloric acid and of 0.9 g. of sodium *p*-fluorophenyl sulfinate in 10 cc. of water were mixed, the resulting thiourea salt filtered and recrystallized from 25 cc. of 0.25 *N* acid, when it separates in elongated prismatic columns showing a melting point of 161° (corr.).

Anal. Calcd. for $C_{14}H_{15}O_2N_2S_2F$: N, 8.6. Found: N, 8.7.

Benzyl-ψ-thiourea Salt of *p*-Fluorophenyl Sulfonic Acid.—A solution of 1 g. of sodium *p*-fluorophenyl sulfinate in 5 cc. of *N* sodium hydroxide was treated dropwise with 5 cc. of 30% hydrogen peroxide, and following the original heating up and gas evolution, it was heated on the steam-bath for one-half hour to complete the oxidation. The oxidized solution was carefully neutralized with *N* hydrochloric acid and added to a solution of 1.1 g. of benzyl-ψ-thiourea hydrochloride in 10 cc. of 0.25 *N* hydrochloric acid. The precipitated salt was filtered and recrystallized from 15 cc. of 0.25 *N* hydrochloric acid, being obtained in brilliant plates, melting at 166° (corr.).

Anal. Calcd. for $C_{14}H_{15}O_3N_2S_2F$: N, 8.2. Found: N, 8.3.

***p*-Fluorophenylphenacyl Sulfone.**—A solution of 1 g. of sodium *p*-fluorophenyl sulfinate in 5 cc. of water and 15 cc. of 95% alcohol was refluxed for fifteen minutes with 1.1 g. of ω-bromoacetophenone and the precipitate which separated on cooling was recrystallized from 30 cc. of 95% alcohol. The sulfone separates in large elongated colorless plates melting at 151° (corr.).

Anal. Calcd. for $C_{14}H_{11}O_3SF$: S, 11.5. Found: S, 11.3.

***p*-Fluorophenyl *p*-Nitrobenzyl Sulfone.**—This sulfone was obtained from the sulfinate and *p*-nitrobenzyl chloride and crystallized from 95% alcohol in slightly yellow briliant plates melting at 185° (corr.).

Anal. Calcd. for $C_{13}H_{10}O_4NSF$: N, 4.8. Found: N, 5.0.

***p*-Fluorophenyl Sulfone Acetic Acid.**—A solution of 3 g. of sodium *p*-fluorophenyl sulfinate and 1.6 g. of monochloroacetic acid in 15 cc. of water was neutralized with *N* sodium hydroxide, evaporated over a free flame to crystallization and then to dryness on the steam-bath. The dry salt was taken up in 10 cc. of water, acidified to Congo red

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[1] Publication authorized by the Surgeon General, U. S. Public Health Service.

[2] Knoevenagel and Kenner, *Ber.*, **41**, 3315 (1908).