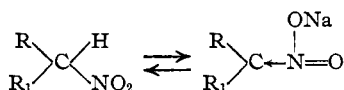


[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

The Asymmetry of the Aliphatic Nitro Group.¹ Resolution of 9-Nitro-2-Benzoylfluorene

BY FRANCIS EARL RAY AND STEPHEN PALINCHAK

The evidence for the asymmetry of the aliphatic *aci*-nitro group is based almost entirely on the conversion of optically active secondary nitro compounds to optically active salts and the reconversion of the salts to active nitro compounds.^{1a} This is represented by the following equation in which the *aci*-form contains a carbon-nitrogen semipolar bond. The fourth group on the asymmetric carbon is an unshared pair of electrons.

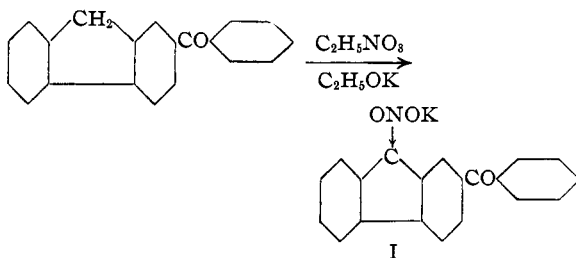


Kuhn and Albrecht found, however, that their active salts contained an excess of sodium ethylate, while Shriner, *et al.*, did not isolate any active salts.

In addition to this well-established evidence, Shriner and Thurston, and Shriner and Parker,² have carried out partial asymmetric syntheses and reported compounds with a trace of activity. Mills³ announced the resolution of phenylcyanonitromethane but no details have ever appeared.

In the present work, our object was to start with an inactive compound and attempt to resolve it by the formation of diastereoisomeric salts of alkaloids.

The compound chosen for study was the potassium salt of 9-nitro-2-benzoylfluorene, I.



It was prepared by the method of Wislicenus⁴ from benzoylfluorene, ethyl nitrate and potassium

(1) Presented before the Division of Organic Chemistry, American Chemical Society, Cincinnati, Ohio, April 9, 1940.

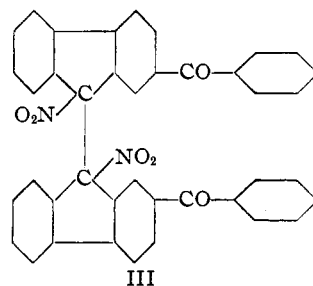
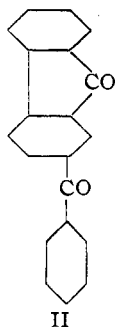
(1a) Kuhn and Albrecht, *Ber.*, **60**, 1297 (1927); Young and Shriner, *This Journal*, **52**, 3332 (1930).

(2) Thurston and Shriner, *ibid.*, **57**, 2163 (1935); Parker and Shriner, *ibid.*, **55**, 766 (1933).

(3) Mills, *J. Soc. Chem. Ind.*, **51**, 750 (1932). Cf. Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., p. 308, for a detailed discussion of the electronic structures involved.

(4) Wislicenus, *Ber.*, **29**, 494 (1896).

ethoxide. This compound and its potassium and alkaloidal salts remained stable for several years. Solutions were less stable and especially an aqueous solution of the potassium salt soon decomposed to give 2-benzoylfluorenone, II. The pale yellow free *aci*-form was obtained on acidification of the potassium salt. On boiling this in alcohol the bright red dimer (melting at 135–137°), III, was obtained. This is similar to the results obtained by Dale and Shriner.⁵



By mixing equivalent warm alcoholic solutions of brucine hydrochloride and potassium 9-*aci*-nitro-2-benzoylfluorene of the proper concentration, it was possible to obtain, by slow crystallization, 50% of the theoretical amount of the brucine nitro salt. It had an initial specific rotation of +75° in chloroform. If two equivalents of brucine hydrochloride were used, about 90% of the theoretical yield was obtained, but the specific rotation of the salt then was only +52° in chloroform. We thought that this might represent the difference in rotation between a single diastereoisomer and a mixture of both diastereoisomers. Both salts contained one mole of base to one of acid so that the excess brucine hydrochloride in the second case acted simply as a "salting out" reagent. Analyses always showed the presence of one mole of alcohol of coordination.

Treatment of the supposedly active brucine nitro salt with potassium ethoxide, or with acids, yielded compounds which were optically inactive. They separated from alcohol *without* alcohol or potassium ethoxide of coordination. In the light of Kuhn and Albrecht's results, this would

(5) Dale and Shriner, *This Journal*, **58**, 1502 (1936).

account for the lack of activity. Unless the "lone pair" of electrons on the asymmetric carbon is strongly coordinated with an acceptor molecule, the compound racemizes.⁶ A dynamic study of the action of the brucine nitro salt on treatment with alcoholic potassium hydroxide was enlightening. Immediately on mixing, the solution had a specific rotation (based on the brucine present) of -65° . At the expiration of four hours the rotation was -75° , and after thirty hours it had become constant at -82.87° . The rotation of free brucine under identical conditions is -83.54° .

The difference of 18° between the initial and final rotations is about the same as observed for the active and inactive brucine salts and is, we believe, the approximate rotation of the 9-*aci*-nitro-2-benzoylfluorene ion. When aqueous potassium hydroxide was used there was no change in rotation with time. If the compound was not resolved, then it must be assumed that the alcoholic potassium hydroxide took about thirty hours to react with the brucine salt of the *aci*-nitro compound whereas aqueous alkali reacted instantly. This assumption is hardly tenable inasmuch as Kuhn and Albrecht found that their salt also possessed no activity when prepared with *aqueous* alkali.

In an attempt to precipitate the active potassium salt under milder conditions, a saturated solution of the brucine salt was treated with an alcoholic solution of potassium acetate. The rotation at the time of mixing was -1.70° . This rose during an hour and fifteen minutes to -1.56° . The potassium salt then began to precipitate out and the rotation slowly fell to -1.65° . The potassium salt was inactive. A possible explanation of this phenomenon is that potassium acetate displaced alcohol of coordination, giving rise to the increase in rotation. The potassium salt then racemized and precipitated from solution without a coordinating molecule.

When a suspension of brucine 9-*aci*-nitro-2-benzoylfluorene was treated with dilute hydrochloric acid, either at room temperature or at -10° , the light yellow *aci*-nitrobenzoylfluorene precipitated. It showed no activity. But when the brucine salt was dissolved in glacial acetic acid, the rotation changed in the course of thirty minutes from $+0.11^\circ$ to -0.08° ($[\alpha]_D + 5.54^\circ$ and -4.04°). Brucine in acetic acid gives a specific

(6) It is true, however, that optically active sulfoxides $R_1R_2S \rightarrow O$ have been isolated in which the asymmetry of the molecule is due to a "lone pair" of electrons.

rotation of -6.00° . This may well indicate that the active *aci*-form is capable of transitory existence in the presence of (coordinated with) acetic acid.

When the brucine salt of our compound was treated with bromine, the halogen was absorbed readily and an active bromide resulted. This racemized rather rapidly and by the end of two hours was inactive, Table I.

TABLE I

C	α_D	t (min.)	$[\alpha]_{30D}$
0.0837 g.	0.72	0	107.5
in 25 cc.	.65	10	97.6
of $CHCl_3$.25	30	37.5
	.00	120	00.0

This may be classed as a partial asymmetric synthesis. Inasmuch as an excess of bromine was used, however, the theoretical conditions necessary for an asymmetric synthesis were not present.

A study of the mutarotation of the supposedly active brucine salt in chloroform was then undertaken. The time plotted against the log of the concentration, one over the concentration, and one over the concentration squared, all failed to yield straight lines. From this we concluded that more than one type of reaction was taking place. An examination of the products showed that decomposition had occurred in addition to possible racemization.

In an attempt to study these two effects, the brucine *aci*-nitro salt was prepared in butyl alcohol solution. It contained butyl alcohol of coordination and the color of the salt and its solution was considerably darker than when obtained from ethyl alcohol. It had an initial specific rotation of about $+66^\circ$ (Fig. 1, curve I), while that from ethyl alcohol was $+75^\circ$ (Fig. 1, curve II). The curves also show a striking difference in the course of the first hour. At the least, this shows the importance of the coordinating molecule of alcohol.

The study of the supposedly single diastereoisomer in comparison with a known mixture of both diastereoisomers, in chloroform solution, led to somewhat inconclusive results although the latter always had a lower initial rotation. If some means could be found to prevent decomposition, the active compound should change in rotation due to racemization, while the mixture of diastereoisomers should have a constant value. After several experiments we found that pyridine

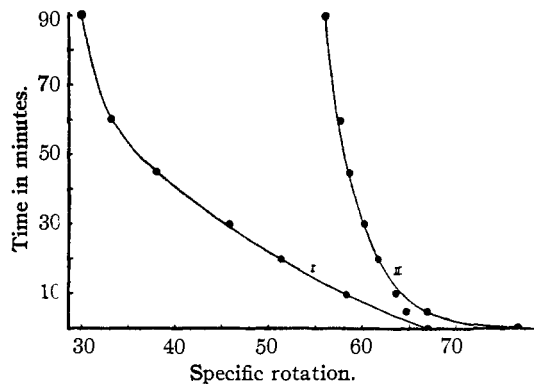


Fig. 1.

effectively stabilized the compounds for about thirty minutes. During this time the active compound racemized, while the mixture of isomers remained unchanged. Decomposition then set in and the curves became much the same as they had been in chloroform. This is graphically shown in Fig. 2, where I represents the single diastereoisomer, while II is the mixture.

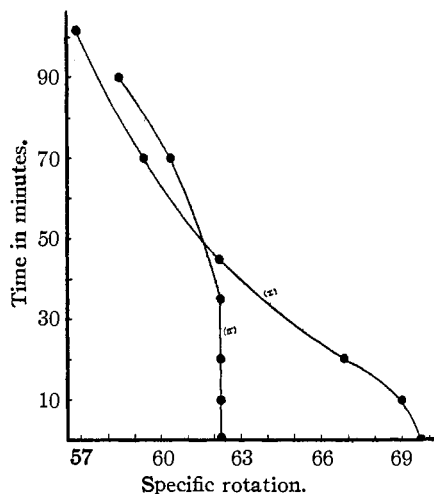
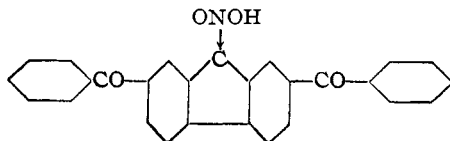


Fig. 2.

That this is truly a racemization is apparent from the calculation of the velocity constants for a monomolecular reaction or by plotting time against $\log \alpha$, Fig. 3.

If our conclusion is correct, symmetrical *aci*-nitro compounds should behave like the mixture of diastereoisomers in pyridine. As a critical test, we prepared and studied the brucine salt of 9-*aci*-nitro-2,7-dibenzoylfluorene under identical conditions.



This salt had a specific rotation of $+67^\circ$ in chloroform and $+78^\circ$ in pyridine. When dissolved in pyridine there was *no* change in rotation for two hours. Decomposition then slowly set in and at the end of six hours the rotation had decreased to $+72^\circ$. This definitely shows that resolution of the 9-*aci*-nitro-2-benzoylfluorene had been accomplished. It eliminates also the possibility of the mutarotation that has been observed for brucine salts by Adams, McKenzie and Kenyon.⁷

A mixture of equivalent quantities of the potassium *aci*-nitro salt and brucine hydrochloride in solution had the same specific rotation as the material precipitated by two equivalents of brucine hydrochloride. This served as a check on the properties of the mixture of diastereoisomers.

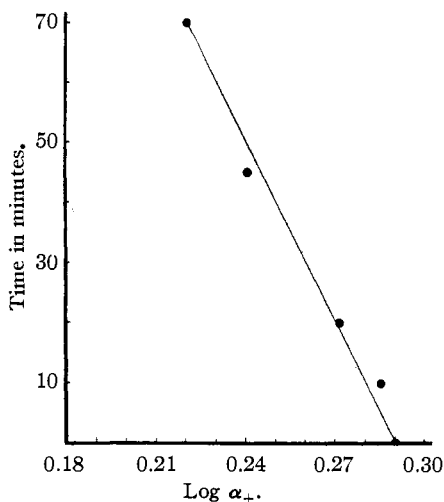


Fig. 3.

Experimental

2-Benzoylfluorene was prepared by Perrier's⁸ method.

Potassium 9-*aci*-Nitro-2-benzoylfluorene.—To 50 cc. of dry ether was added 14.5 g. of clean potassium. Then 100 cc. of absolute alcohol was dropped in. When the potassium was completely dissolved, a solution of 100 g. of 2-benzoylfluorene and 35 cc. of ethyl nitrate in 500 cc. of benzene was added. The reaction mixture darkened and an orange colored product precipitated. After twelve hours the precipitate was filtered and washed with benzene. It was quite soluble in pyridine, fairly soluble in water and alcohol and practically insoluble in benzene and ether. Yields were 83 to 88%.

Anal. Calcd. for $C_{20}H_{12}NO_3K$: N, 3.96; K, 11.07. Found: N, 3.69; K, 11.11.

It was very stable when dry but in solution was slowly

(7) Hyde and Adams, *THIS JOURNAL*, **50**, 2502 (1928); McKenzie, *J. Soc. Chem. Ind.*, **51**, 491 (1932); Pickard and Kenyon, *J. Chem. Soc.*, **105**, 830 (1914).

(8) Perrier, *Bull. soc. chim.*, (3) **31**, 859 (1904).

oxidized to 2-benzoylfluorenone and nitrous acid. On acidifying an aqueous solution of the potassium salt, the *aci*-form of the free nitro compound was precipitated. It was a pale lemon yellow compound that melted at 80–84° with decomposition. It was readily reconverted to its salts with dilute alkalis. It was insoluble in water, but soluble in alcohol and most other organic solvents.

When boiled in alcohol for ten to fifteen minutes, the pale yellow color changed to red and a red product was deposited on cooling. This melted at 135–137° and was the dimolecular compound, III.⁵

Anal. Calcd. for C₄₀H₂₄N₂O₆: mol. wt., 628. Found: (cryoscopic determination made in benzene) mol. wt., 611.

Resolution of 9-*aci*-Nitro-2-benzoylfluorene.—An attempt was made to prepare an ester of this compound with menthyl bromide in alcoholic solution. The reaction took place but the product was an unstable liquid unsuitable for our purpose. The rotation is given, however, as a means of identification: 0.1941 g. in 10 cc. of alcohol in a 2-dm. tube gave $\alpha_D -8.47^\circ$, $[\alpha]^{24}_D -218^\circ$. Menthyl bromide under the same conditions gave $[\alpha]^{24}_D -81.42^\circ$; menthol, $[\alpha]^{24}_D -50.6^\circ$.

On removal of the alcohol, which apparently stabilized it, the oil decomposed, giving menthol, 2-benzoylfluorenone (II) and the dimolecular compound (III). The compounds were identified by direct comparison with authentic samples.

Resolution was also attempted with cinchonine, quinine and strychnine, without securing a satisfactory crystalline salt.

The brucine salt was prepared by treating potassium 9-*aci*-nitro-2-benzoylfluorene (10 g.) in 500 cc. of 95% ethyl alcohol at 70° with 12.2 g. (one equivalent) of brucine hydrochloride in 80 cc. of alcohol at 50°. As the solution cooled, crystals slowly formed. After about half an hour they had settled and were filtered, washed with water until free from chloride ion, and air dried. The yield was 11.1 g. or 50%. The brilliant yellow crystals sintered at 160° and melted with decomposition at 175–185°. In 25 cc. of anhydrous chloroform, 0.3943 g. in a 2-dm. tube gave $\alpha_D +2.38^\circ$; $[\alpha]^{23}_D +75.39^\circ$.

Anal. Calcd. for C₄₃H₃₉O₇N₃·C₂H₅OH: C, 71.50; H, 5.96. Found: (six determinations) C, 71.84; H, 5.93. Without the alcohol of coordination the figures require: C, 72.77; H, 5.50.

A sample of the brucine salt (1.0021 g.) was treated with an excess of 0.2 *N* sodium hydroxide and extracted with benzene. The observed specific rotation calculated on the basis of one mole of brucine to one mole of *aci*-nitro compound was -97.3° . On the basis of two moles of brucine to one of *aci*-nitro the rotation would be -71.14° . Pure brucine under the same conditions gave -102.9° , thus showing that a 1-1 salt was obtained.

Action of Alcoholic Potassium Hydroxide on the Brucine Salt.—A sample of 0.7898 g. of the brucine salt in 25 cc. of 5% alcoholic potassium hydroxide gave the rotations recorded in Table II. The specific rotations were calculated on the amount of brucine present. Pure brucine under the same conditions gave $\alpha_D -2.94^\circ$ for a sample of 0.4398 g. or $[\alpha]^{23}_D -83.34^\circ$.

Action of Potassium Acetate on the Brucine Salt.—A solution of 0.5595 g. of the brucine salt in chloroform was treated with a saturated solution of potassium acetate in

TABLE II

Time in hours	α_D	$[\alpha]^{23}_D$
0:00	-2.15	-65.02
3:25	2.35	71.06
4:45	2.50	75.60
23:55	2.70	81.66
39:55	2.74	82.87

TABLE III

Time in hours	α_D
0:00	-1.70
0:15	1.62
1:15	1.56
17:45 ppt.	1.58
22:15 ppt.	1.61
65:45 ppt.	1.65

n-butyl alcohol. The rotations were measured in a 2 dm. tube at 23°. The crystals which began to precipitate after seventeen hours were filtered off, but they were inactive. Attempts to obtain the active solid quickly by cooling were unsuccessful. It appears that the active compound is more soluble than the racemic.

Anal. Calcd. for C₂₀H₁₂O₃NK: K, 11.05. Found: K, 11.05, 10.96.

Action of Glacial Acetic Acid on the Brucine Salt.—A sample of 0.4735 g. of brucine 9-*aci*-nitro-2-benzoylfluorene, equivalent to 0.2478 g. of brucine, gave the rotations recorded in Table IV when dissolved in 25 cc. of glacial acetic acid and measured in a 2-dm. tube. Brucine dis-

TABLE IV

Time in hours	α_D	$[\alpha]^{24}_D$
0:00	+0.11	+5.54
0:35	- .09	-4.04
21:45	- .08	-4.04

solved in glacial acetic acid did not mutarotate but gave a constant specific rotation of -6.00° .

Bromination of the Brucine Salt.—To 0.15 g. of the brucine salt 10 cc. of cold chloroform was added. After cooling in an ice-bath, a 20% solution of bromine in chloroform was added slowly until the brown color persisted. The brucine hydrobromide was removed by washing four times with water. The chloroform solution was quickly dried and the rotation taken, Table I. The compound on isolation varied in composition. Attempts to recrystallize it resulted in the formation of 2-benzoylfluorenone. Lack of material prevented further study of this compound.

Brucine 9-*aci*-Nitro-2,7-dibenzoylfluorene.—The 2,7-dibenzoylfluorene was prepared similarly to the monobenzoylfluorene, using two equivalents of benzoyl chloride and two equivalents of aluminum chloride. The yield was 36% of a compound melting at 194–195°. From the mother liquor there was obtained a compound melting at 119–120° which may be 2,3-dibenzoylfluorene. It has not yet been further examined.

Potassium 9-*aci*-nitro-2,7-dibenzoylfluorene was prepared similarly to the monobenzoyl compound. It was obtained in yields of 65% and was redder in color than the monobenzoyl salt.

(9) Dziewonski and Obtulowicz, *Bull. intern. l'acad. polon. sci., Classe sci. math. nat.*, A, 399 (1930).

Anal. Calcd. for $C_{27}H_{16}O_4NK$: K, 8.56. Found: K, 8.73.

When recrystallized from *n*-butyl alcohol we obtained flaky red crystals which contained alcohol of crystallization. Had this been the case with the mono-benzoyl compound we might have been successful in isolating it in an active state.

Anal. Calcd. for $C_{27}H_{16}O_4NK \cdot C_4H_9OH$: K, 7.35. Found: K, 7.06, 7.15.

To a boiling filtered solution of 5 g. of potassium 9-*aci*-nitro-2,7-dibenzoylfluorene in 400 cc. of ethyl alcohol was added 4.74 g. of brucine hydrochloride in 100 cc. of alcohol. When mixed the temperature was 80°. On cooling to 50°, crystals began to separate when the sides of the container were scratched. The solution had been red but turned yellow when crystallization took place.

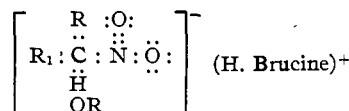
The solid was filtered and triturated with water to remove potassium chloride, washed with alcohol and dried in air. The yield was 5 g. or 51%.

A sample of 0.2204 g. in 25 cc. of chloroform in a 2-dm. tube gave $\alpha_D +1.18^\circ$, $[\alpha]_D^{25} +66.92^\circ$. In pyridine there was no mutarotation over a period of two hours; the specific rotation then slowly changed from $+78.07^\circ$ to $+72.56^\circ$ in the course of six hours.

Summary

We have presented evidence to show that the resolution of the 9-*aci*-nitro-2-benzoylfluorene ion into its antipodes has been accomplished with brucine.

The brucine salt contains alcohol of crystallization which we think accounts for its activity by stabilizing the "lone pair" of electrons as follows. This structure is similar to that sug-



gested by Young and Shriner¹ for the coördination compound of the sodium salt of 2-nitroöctane and alcohol.

Neither the free 9-*aci*-nitro-2-benzoylfluorene nor its potassium salt crystallized with alcohol of coördination and neither could be obtained in an active form, although in solution both showed a transitory activity.

The symmetrical compound, 9-*aci*-nitro-2,7-dibenzoylfluorene, has been prepared and found to differ radically in optical properties from the unsymmetrical 9-*aci*-nitro-2-benzoylfluorene.

If an *aci*-nitro compound or its salt can be obtained that separates with a coördinating molecule, we predict that the application of the technique here described will result in its isolation in an optically active form.

CINCINNATI, OHIO

RECEIVED JUNE 13, 1940

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CORN PRODUCTS REFINING COMPANY]

The Reduction of Aldoses at the Dropping Mercury Cathode: Estimation of the *aldehydo* Structure in Aqueous Solutions¹

BY SIDNEY M. CANTOR AND QUINTIN P. PENISTON

Investigations on aqueous solutions of the reducing sugars at equilibrium rotation have demonstrated that a condition of dynamic equilibrium between several components is involved and that, depending on conditions and reagents, the equilibrium may be shifted to form derivatives of several parent structures. While it has been possible to estimate from various data the relative amounts of alpha and beta pyranose forms for certain of the aldoses at equilibrium, it has hitherto not been possible to measure the concentration of or indeed adequately to demonstrate the presence of the so-called "free aldehyde" or *aldehydo* structure. Such a non-cyclic tautomer must necessarily be postulated as the intermediate through which

mutarotation, ring shift and other structural transformations occur.

Indications that more than two isomers are concerned in the mutarotation of the reducing sugars are contained in the extensive researches of the Lowry, Hudson and Isbell² groups. While the first order mechanism adequately represents the data obtained in some cases, in other cases this interpretation does not hold and the mutarotation can only be described as anomalous.

Several attempts have been made to establish the *aldehydo* structure. Thus, ultraviolet studies on aldose solutions originally conducted by Niederhoff³

(1) Presented at the Cincinnati meeting of the American Chemical Society, April 10, 1940.

(2) (a) Lowry, *J. Chem. Soc.*, 1913 (1903); Lowry and Richards, *ibid.*, 1385 (1925); Smith and Lowry, *ibid.*, 666 (1928); (b) Hudson, *Sci. Pap. Bur. Standards* No. 533 (1926); (c) Isbell and Pigman, *J. Research Natl. Bur. Standards*, **18**, 141 (1937).

(3) Niederhoff, *Z. physiol. Chem.*, **165**, 130 (1927).