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Studies on the Chemistry of Heterocyclics. XXXI.[1] Bi-Aromatics in the Thiophene Series. IV. The Resolution and Racemization of a β-Phenylthiophene Exhibiting Restricted Rotation

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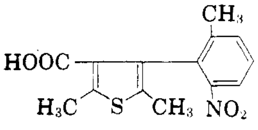
A β-phenylthiophene exhibiting restricted rotation was successfully resolved through its brucine salts which were fractionally crystallized from 50% aqueous ethanol. The optically active acids were isolated upon hydrolysis of their respective brucine salts, and their effect on the melting point of the *dl*-acid was studied. The brucine salt with the lower rotation gave the *l*-acid; an opposite direction in the rotation of the free *d*-acid as compared with its respective brucine salt was observed.

The optically active acids were stable in chloroform and methanol at room temperature for at least one week and in glacial acetic acid for at least 24 hours under the same conditions, but partial racemization occurred during attempts to recrystallize them from boiling methanol. The racemization of the *l*-acid was studied in boiling chloroform, methanol, and glacial acetic acid and the respective half-life periods for the compound in the three solvents were determined; it racemized more rapidly in boiling acetic acid than it did in the lower-boiling solvents.

The optical stability of this compound as compared with its biphenyl, α-phenylthiophene, and β-phenylfuran analogs is discussed and a possible explanation offered for the significant differences observed.

In a previous communication from this laboratory,[3] the preparation of a β-phenylthiophene containing four *ortho* substituted groups was recorded, thus rendering possible the study of restricted rotation in a heretofore unavailable field. In a subsequent paper,[4] it was also demonstrated that studies of the ultraviolet absorption spectra of this compound and of related types indicate the existence of non-coplanar forms due to steric hinderance caused by the bulky *ortho* groups. The present report is concerned with the resolution of 2,5-dimethyl-4-(6′-methyl-2′-nitrophenyl)-3-thenoic acid and the racemization of its optical antipodes.

In the light of our basic assumptions previously discussed,[5] the interference value for this compound



was calculated and found to be +0.49 Å which is sufficiently large to enable the isolation of enantiomorphic forms. Similar calculations for the β-bithienyl and biphenyl analogs resulted in values of +0.44 Å and +0.57 Å respectively. In these calculations the accepted internuclear distances between the 2,2′-carbon atoms and the *ortho* substituted atoms or groups were applied.[6] The distance between the centers of the 2,2′-carbon atoms in a coaxial, coplanar model of biphenyl is known to be 2.90 Å, while the corresponding distances in the case of the β-bithienyl and β-phenylthiophene were calculated using trigonometric means. It is noteworthy that on an empirical basis, when the interference value is +0.39 Å or more, complete rotation is rendered impossible in the biphenyl series.

RESULTS

2,5-Dimethyl-4-(6′-methyl-2′-nitrophenyl)-3-thenoic acid was successfully resolved through its brucine salts which were fractionally crystallized from 50% aqueous ethanol. The diastereoisomers so obtained then were further purified until their melting points and optical rotations were constant. The more insoluble salt gave a specific rotation in chloroform of $[\alpha]^{25^\circ}_{D}$ −30.56°, while the more soluble fraction possessed a value of $[\alpha]^{25^\circ}_{D}$ −54.86°.

Hydrolysis of the brucine salts was accomplished using ice-cold 6 *N* HCl to afford the desired optically active acids. The latter were studied polarimetrically in two different solvents. The data are summarized in Table I. It should be kept in mind that the brucine salt with the lower reading gave the *l*-acid. Furthermore, the observation of an opposite direction in the rotation of the free acid as compared with the brucine salt from which it is derived, is not an uncommon occurrence.[5,7,8]

TABLE I

PHYSICAL PROPERTIES OF THE OPTICAL ISOMERS

Optical Antipode	M.P., °C.	$[\alpha]^{25^\circ}_{D}$ ($CHCl_3$)	$[\alpha]^{25^\circ}_{D}$ (MeOH)
l-acid	208–210	−4.21°	−3.91°
d-acid	209–211	+3.24°	+3.31°

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(1) For the previous communication of this series see: Jean and Nord, *J. Org. Chem.*, **20**, 1370 (1955).

(2) Abridged from a portion of the dissertation submitted by the author in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Fordham University.

(3) Jean and Nord, *J. Org. Chem.*, **20**, 1363 (1955).

(4) Jean and Nord, *J. Org. Chem.*, **20**, 1370 (1955).

(5) Owen and Nord, *J. Org. Chem.*, **16**, 1864 (1951).

(6) Gilman, *Organic Chemistry*, 1st ed., John Wiley and Sons, New York, N.Y., 1938, p. 268.

(7) Leslie and Turner, *J. Chem. Soc.*, 347 (1934).

(8) Khawam, Doctoral Dissertation, Fordham University, 1953.

In the course of these studies, it was noted that recrystallization of the optical isomers from boiling methanol caused partial racemization to occur, but the methanol solutions were stable for at least one week at room temperature, as were the chloroform solution; the *l*-acid was stable in glacial acetic acid for at least 24 hours under the same conditions.

Inasmuch as melting point determinations and other applications of the Phase Rule serve to differentiate between a racemic mixture and a racemic compound,[9] it was decided to study the effect of the optical antipodes on the melting point of the *dl*-acid. It was found that on admixture with an equal amount of either enantiomorph the melting point of the racemic modification was depressed, thus indicating that the *dl*-acid is a racemic compound.

Before proceeding to the racemization studies, it should be mentioned that estimated interference values do not always serve as a reliable guide in predicting racemization rates in view of the fact that it has been reported that half-life periods change with the solvents used;[10] hence, the effective sizes of the groups must be somewhat dependent on their solvation. Undoubtedly, factors such as the entropy of activation for racemization are of considerable importance.

Accordingly, the half-life period of the *l*-acid was determined in three different solvents in an endeavor to study the influence of solvent on the racemization rate. The solvents selected were chloroform, a non-hydroxylated solvent with a low dielectric constant; methanol, a hydroxylated solvent boiling in the same range with a high dielectric constant; and glacial acetic acid, a higher-boiling hydroxylated solvent with a low dielectric constant. At room temperature, the *l*-acid did not racemize appreciably in all three solvents, but racemization did not occur at their boiling points and the corresponding half-life periods were determined. In this connection, it was reported[11] that the decrease in optical activity of biphenyls was a first order reaction. This furnished at least a semiquantitative measure of the stability of such compounds under different conditions. In Table II the kinetics of racemization together with the half-life periods for the *l*-acid under different conditions are summarized:

TABLE II

RATES OF RACEMIZATION FOR *l*-2,5-DIMETHYL-4-(6′-METHYL-2′-NITROPHENYL)-3-THENOIC ACID UNDER DIFFERENT CONDITIONS

Solvent	Temp., °C.	Initial $[\alpha]^{25°}_{D}$	Aver. K	Aver. Dev.	$T_{\frac{1}{2}}$ (min.)
$CHCl_3$	61	−4.21°	0.02385[a]	±0.00158	29.6
MeOH	65	−3.91°	.02835[b]	±0.00165	24.4
HOAc	118	−5.27°	.23934[c]	—	2.9

[a] Average of 5 values. [b] Average of 4 values. [c] Only one determination of K could be made in boiling glacial HOAc. See Experimental.

As can be seen from these data, the solvent medium has not changed the initial readings at room temperature to any considerable extent. Also, the half-life periods for the *l*-acid in boiling chloroform and methanol are essentially the same, facts which are in accord with their similar boiling points. However, the rate of racemization in boiling glacial acetic acid was almost ten times as fast as it was in the lower-boiling solvents. Hence, the influence of temperature appears to be the primary consideration in studies of this type rather than solvolytic effects. Inasmuch as raising the temperature by 10° approximately doubles the reaction rate, such a qualitative difference in the half-life is to be expected.

DISCUSSION

It should be noted that the half-life period for 2-methyl-6-nitro-2′-carboxybiphenyl in boiling glacial acetic acid was 34 hours.[12] On the other hand, 2-(6′-methyl-2′-nitrophenyl)-3-thenoic acid racemized in methanol at room temperature after one hour.[5] The furan analog of our compound racemized completely in boiling ethanol during recrystallization.[8] It is evident from the differences in the optical stability of the parent biphenyl as compared with its heterocyclic analogs that the phenyl moiety is not exchanged for 2-thienyl, 3-furyl, or 3-thienyl moieties without a concomitant change in the properties of the molecule. An explanation for this might be the fact that the bond angles and distances are somewhat different in the mixed biaromatics or that the length of the pivot bond is somewhat more than the assumed value of 1.48 Å which is found in biphenyl. The above data together with the calculated interference values for these compounds are listed in Table III.

In conclusion, it can be deduced from the data here presented that the kinetic properties of 2,5-dimethyl-4-(6′-methyl-2′-nitrophenyl)-3-thenoic acid are not completely in accord with what might be predicted from X-ray data; the compound we have described is more easily racemized than the biphenyl analogue. This might be explained in the light of the reasoning outlined previously.

EXPERIMENTAL

Materials. The preparation and purification of *dl*-2,5-dimethyl-4-(6′-methyl-2′-nitrophenyl)-3-thenoic acid, m.p. 211–212°, has been described elsewhere.[3,4] Anhydrous *l*-brucine (highest purity) was obtained from commercial sources and used in the resolution studies without further purification. The chloroform (containing ethanol as a stabilizer) and methanol employed as solvents for the polari-

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[9] Roozeboom, *Z. physik. Chem.*, **28,** 494 (1899).

[10] Adams, *et al.*, *J. Am. Chem. Soc.*, **57,** 1565 (1935); **61,** 2825 (1939); **61,** 2828 (1939).

[11] Kuhn and Albrecht, *Ann.*, **455,** 272 (1927); **458,** 221 (1927).

[12] Stoughton and Adams, *J. Am. Chem. Soc.*, **52,** 5263 (1930).

TABLE III

RATES OF RACEMIZATION AND INTERFERENCE VALUES FOR 2,5-DIMETHYL-4-(6′-METHYL-2′-NITROPHENYL)-3-THENOIC ACID AND RELATED COMPOUNDS

Moiety	Calc'd I. V.[a]	Solvent	Temp., °C.	Antipodal Stability
Phenyl	+0.18 Å	HOAc	118	Half-life, 34 hours
2-Thienyl[b]	—	CH_3OH	25	Racem. after 1 hour
3-Furyl	+0.45 Å	EtOH	78	Racem. after recryst.
3-Thienyl	+0.49 Å	HOAc	118	Half-life, 2.9 min.

[a] I. V. = interference value. [b] The interference value for the α-phenylthiophene cannot be calculated on the same basis as the other bi-aromatics inasmuch as the sulfur atom cannot possess a substituted group; hence, the use of an internuclear distance value is rendered impossible. However, it is significant in this connection that Price, Mertz, and Wilson, *J. Am. Chem. Soc.*, **76**, 5131 (1954) have ascribed the unexpected slow saponification of ethyl 2-thenoate to stearic hindrance on the part of the sulfur atom.

metric determination were both of C.P. grade, while the glacial acetic acid (99.5%) was U.S.P.

Apparatus. The melting points as reported are uncorrected and were obtained with a Fisher-Johns melting point block. All optical rotations were determined in a 1.0-dm. nickel-jacketed polarimeter tube by means of a Rudolph universal high-precision polarimeter, Model 80, equipped with a sodium vapor lamp as the light source. Water was circulated through the tube which was connected to a constant temperature bath thermostated at 25°.

Procedure. All optical rotations were obtained at 25° by first immersing the solutions in a constant temperature bath thermostated at this point; temperature control in the solutions is estimated at ±0.5°.

Observed rotations represent the average of duplicate values agreeing generally within ±0.002°, except where larger deviations were encountered whereupon six readings were taken. All readings were corrected with respect to zero points obtained with solvent blanks.

Resolution. dl-2,5-Dimethyl-4-(6′-methyl-2′-nitrophenyl)-3-thenoic acid (0.437 g., 0.0015 *M*) and anhydrous *l*-brucine (0.591 g., 0.0015 *M*) were dissolved in 100 ml. of 50% aqueous ethanol which had been brought to a gentle boil. The resulting solution was stirred continuously for 10 minutes and then was allowed to cool to room temperature and was placed in the refrigerator. At the end of three days a gum-like material had precipitated. After suction filtration it was washed with cold ethanol and air-dried. The salt then was placed in a vacuum desiccator over silica-gel for 24 hours. The hardened material now could be powdered to a crystalline form and it weighed 0.484 g. After two recrystallizations from ethanol, the melting point was constant, 115–117° (after first softening at 109°), as was the rotation; the latter was determined after the salt had been dried *in vacuo* at room temperature for 24 hours. The microanalytical sample was recrystallized again from ethanol and then from acetone and finally was dried *in vacuo* over P_2O_5 at 100° for 8 hours.

Rotation. Less soluble salt (*l*-brucine, *l*-acid): 0.0986 g. made up to 10 ml. with chloroform at 25° gave α_D −0.301°, $l = 1$; $[\alpha]^{25°}_{D}$ −30.56°.

Anal. Calc'd for $C_{37}H_{39}N_3O_8S$: N, 6.13. Found: (Micro Dumas) N, 6.21.

The filtrate was evaporated *in vacuo* almost to dryness and then was cooled in an ice-bath. There was obtained a gum-like material which appeared to be slightly more crystalline than the precipitate of the less soluble salt. After suction filtration and drying *in vacuo* over silica-gel the material could be powdered to a crystalline form; it weighed 0.263 g. It is of interest to note that this fraction appeared to be distinctly less yellow in color than its diastereoisomer. After two recrystallizations from ethanol it gave a constant melting point, 114–116° (after first softening at 109°), and rotation. The same procedure was followed for the preparation of the microanalytical sample as in the case of its diastereoisomer.

Rotation. More soluble salt (*l*-brucine, *d*-acid): 0.0735 g. made up to 10 ml. with chloroform at 25° gave α_D −0.403°, $l = 1$; $[\alpha]^{25°}_{D}$ −54.86°.

Anal. Calc'd for $C_{37}H_{39}N_3O_8S$: N, 6.13. Found: (Micro Dumas) N, 6.34.

Both brucine salts were found to be stable inasmuch as they could be recrystallized, their color did not change on standing in the sunlight, and their solutions did not mutarotate.

l-2,5-Dimethyl-4-(6′-methyl-2′-nitrophenyl)-3-thenoic acid. The less-soluble brucine salt (0.300 g.) was treated with 15 ml. of ice-cold 6 *N* HCl at 0° with vigorous stirring. After 30 minutes the precipitated acid was filtered, washed with a small amount of 2 *N* HCl, until the washings gave a negative test for brucine, and then with sufficient ice-cold water to remove any trace of inorganic acid. After drying in a vacuum desiccator the product amounted to 0.112 g. and melted at 208–210° with softening at 203°. A depression in the melting point of the racemic acid (m.p. 211–212°) could be observed on admixture with an equal amount of the *l*-acid (mixture m.p. 202–204° after first softening at 194°).

Rotation. 0.0895 g. of the *l*-acid made up to 10 ml. with methanol at 25° gave α_D −0.035°, $l = 1$; $[\alpha]^{25°}_{D}$ −3.91°.

The optical rotation remained essentially the same after standing at room temperature, but attempts to recrystallize the material from boiling methanol caused partial racemization to occur. The *l*-acid therefore was dissolved in dry acetone at room temperature, and an excess of petroleum ether (b.p. 20–40°) was added; after standing in the refrigerator overnight, a small amount of the acid crystallized out as a flaky material. However, the melting point and rotation were unchanged by this treatment.

d-2,5-Dimethyl-4-(6′-methyl-2′-nitrophenyl)-3-thenoic acid. The more-soluble brucine salt (0.120 g.) was decomposed in the usual manner with ice-cold 6 *N* HCl to afford 0.041 g. of the *d*-acid, m.p. 209–211° with softening at 204°. A depression in the melting point of the racemic acid (m.p. 211–212°) could be observed on admixture with an equal amount of the *d*-acid (mixture m.p. 203–205° with softening at 196°).

Rotation. 0.0332 g. of the *d*-acid made up to 10 ml. with methanol at 25° gave α_D +0.11°, $l = 1$; $[\alpha]^{25°}_{D}$ +3.31°.

A mixture of equal amounts (0.010 g.) of the *d*- and *l*-acids was prepared; it melted at 210–211° with softening at 204°. Its chloroform solution was optically inactive.

RACEMIZATION STUDIES

Polarimetric rate measurements. These experiments all were conducted by refluxing the solutions in an apparatus equipped with ground-glass joints for the desired time periods and then instantly cooling the removed sample by means of an ice-bath. The solution then was placed in a 10-ml. volumetric flask, made up to the mark with solvent at 25°, and thermostated at this point *via* a constant temperature bath.

Method of calculation. From the rotation values at different time intervals, the constant K of the rate of racemization can be calculated from the following formula on the basis of a first order reaction:

$$K = \frac{2.3}{t} \log \frac{\alpha_0 - \alpha_f}{\alpha_t - \alpha_f}$$

where t is the time in minutes, α_0 is the initial rotation and α_t is the rotation at time t (α_f, the final rotation, is zero in the case of racemization studies).

The half-life period is calculated from the equation

$$T_{\frac{1}{2}} = \frac{2.3}{K} \log 2$$

Racemization experiments. Several duplicate experiments gave consistent values. The following are typical experiments.

1. The *l*-acid was racemized in methanol at 65°. The optical rotation of this solution has already been described in the resolution procedure. After 10 minutes of refluxing, the specific rotation was −3.02°; after 20 minutes, −2.24°; 30 minutes, −1.68°; and after 45 minutes −1.23°. Calculated half-life, 24.4 minutes.

2. The *l*-acid was racemized in chloroform at 61°.

Rotation. 0.0617 g. of the *l*-acid made up to 10 ml. with chloroform at 25° gave α_D −0.026°, $l = 1$; $[\alpha]_D^{25^\circ}$ −4.21°.

The optical rotation of this solution did not change appreciably on standing at room temperature for one week ($[\alpha]_D^{25^\circ}$ −3.99°). After refluxing for 10 minutes, the specific rotation was −3.40°; after 20 minutes, −2.59°; 30 minutes, −1.95°; 45 minutes, −1.46°; and after 60 minutes, −1.13°. Calculated half-life, 29.6 minutes.

3. The *l*-acid was racemized in glacial acetic acid at 118°.

Rotation. 0.0835 g. of the *l*-acid dissolved in glacial acetic acid at 25° and made up to 10 ml. gave α_D −0.044°, $l = 1$; $[\alpha]_D^{25^\circ}$ −5.27°.

The rotation was essentially the same after 24 hours, but attempts to recrystallize the *l*-acid from this solvent caused complete racemization. After refluxing for 10 minutes, the specific rotation was −0.48°; after 20 minutes, it was completely racemized. Calculated half-life, 2.9 minutes.

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