[CONTRIBUTION NO. 237 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY AND ENZYMOLOGY, FORDHAM UNIVERSITY]

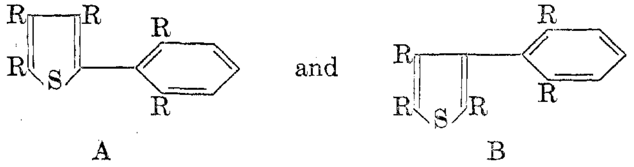
STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XVIII. MIXED BI-AROMATICS I. THE SYNTHESIS AND RESOLUTION OF 2-(6-METHYL-2-NITROPHENYL)-3-THENOIC ACID

LOUIS J. OWEN AND F. F. NORD[1, 2]

Received July 31, 1951

The phenomenon of restricted rotation in the biphenyl series has been amply demonstrated by numerous workers (1, 2a). Adams has extended the scope of this principle to the N,N′-dipyrryls (2b) but attempts to isolate optically active forms of substituted phenylpyridines were unsuccessful (2c). There remained to be explored, however, a variety of "mixed aromatics" in which one component of the bi-aromatic was an heterocyclic ring.

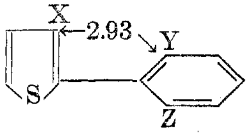
As a natural corollary to our investigations in this series (3), a study was begun which had as its purpose the synthesis and resolution of a phenylthiophene capable of existing in two optical forms due to restricted rotation about its pivot bond. Two possibilities for this phenylthiophene existed:



in which the R's are either hydrogen atoms or groups of sufficient size to obstruct rotation. The present paper is concerned with a bi-aromatic of the type A. An investigation of a phenylthiophene represented by type B is in progress and shall be reported at a later date.

The decision concerning the nature of the groups which should appear on the thiophene and the benzene rings hinged on four basic assumptions: *i.e.* a. The normal bond angles in each ring are not altered, b. the bond connecting the two rings bisects the 120° angle in the benzene ring and the 112° angle (4) in the thiophene ring (the two rings are "coaxial"), c. the length of the carbon-carbon bond which connects the rings is 1.48 Å, and d. the unsubstituted phenylthiophene molecule is coplanar.

On the basis of these assumptions, the α,α'-distance between the two rings was calculated and found to be 2.93 Å (as compared with the value 2.90 Å for biphenyl obtained by x-ray data).



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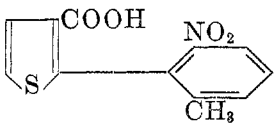
[1] This investigation was carried out under the aegis of the Office of Naval Research. The analyses were obtained through the courtesy of A. A. Sirotenko of this department.

[2] For paper XVII of this series see Miller and Nord, *J. Org. Chem.*, **16**, November 1951.

If, then, the sum of the atomic (or group) radii of X and Y, on the one hand, and the sum of X and Z, on the other, exceeds the value of 2.93 Å by a sufficient margin, resolution of the compound should be possible (2d). In addition to these restrictions, it was necessary to consider the ease with which the thiophene moiety could be synthesized and then made to condense with the suitably substituted benzene portion. The following compound seemed to meet all the requirements:



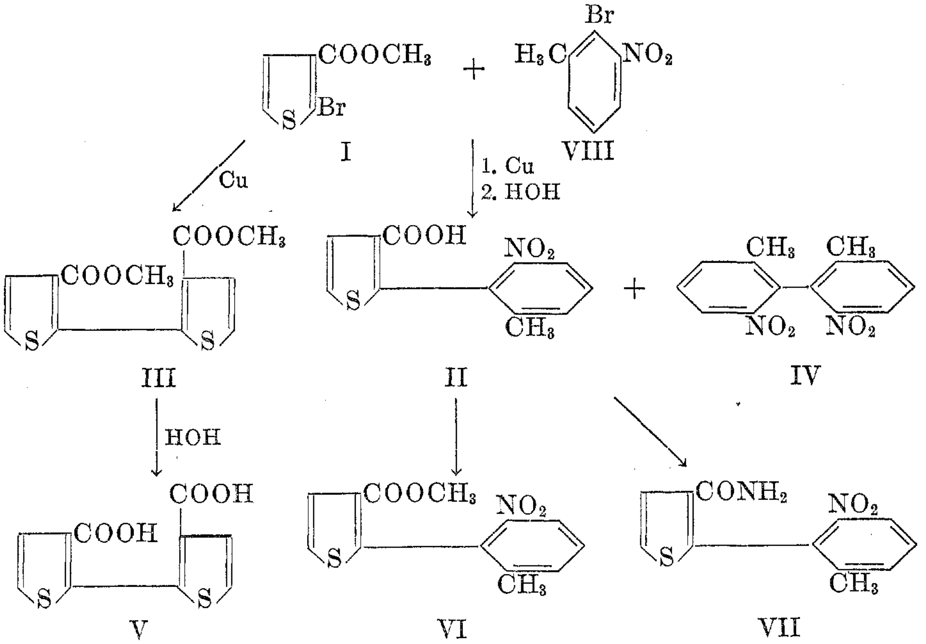
For this structure the sum of the radii of X and Y is 3.48 Å and the sum of the radii of X and Z is 3.29 Å. The interference values are 0.55 Å and 0.36 Å respectively and are sufficiently large to enable the isolation of optical antipodes.

Having accomplished the resolution, it was found, however, that only one brucine salt could be isolated and that it mutarotated rapidly in solution from an initial reading of $[\alpha]_D^{20}$ +30.35° to a final activity of $[\alpha]_D^{20}$ −28.55°. The acid which was isolated from this salt racemized to zero from an initial activity of $[\alpha]_D^{20}$ −11.19°. The observation of an opposite direction in the rotation of the free acid as compared with the brucine salt from which it was isolated is not an uncommon occurrence (5). The brucine salt which was obtained from the filtrate after the insoluble salt was removed gave rise to an inactive acid. This is undoubtedly due to mutarotation taking place while the volume of the solution was being reduced in order to isolate the more soluble salt.

It is evident from the differences in the stability of this phenylthiophene and its biphenyl analogue (2e) that a benzene ring is not exchanged for a thiophene ring without a concomitant change in the properties of the molecule. One explanation for this change, providing the four original assumptions are valid, is that the electron-releasing ability of the hetero-sulfur atom effects a change in the valence angle between the β-carbon atom and the carbon atom of the carboxyl group. It is easily seen that if the carboxyl group were moved away from the benzene moiety, the interference values which were calculated would have no meaning. In this connection, it is interesting to note that in a systematic study (2f, g, h) of the effect of substituents in the 3, 4, and 5 positions on the racemization of 2-nitro-6-carboxy-2′-methoxybiphenyl, it was found that for a series of increasing electron-releasing substituents, the tendency of the compound to racemize increased.

Prior to undertaking the synthesis of 2-(6-methyl-2-nitrophenyl)-3-thenoic acid (II) it was thought necessary to characterize the one unknown byproduct of the proposed Ullmann reaction, 3,3′-dithenic acid (V). This was accomplished by esterifying 2-bromo-3-thenoic acid (6, 7) with diazomethane and treating the resulting ester (I) with copper. The methyl 3,3′-dithenate (III) was hydrolyzed to give the dithenic acid (8).

Methyl 2-bromo-3-thenoate and 3-nitro-2-bromotoluene (2e) (VIII) were then



subjected to the action of copper. The resulting ester and byproducts were hydrolyzed, whereupon the desired acid was obtained. One expected byproduct, 2,2′-dimethyl-6,6′-dinitrobiphenyl (IV) was obtained and discarded, but no 3,3′-dithenic acid was detected. This was probably due to the fact that 3-nitro-2-bromotoluene was used in excess. Further characterization of 2-(6-methyl-2-nitrophenyl)-3-thenoic acid was accomplished by converting it into the methyl ester (VI) and the amide (VII).

EXPERIMENTAL[3]

Methyl 2-bromo-3-thenoate. First, 15 g. of 2-bromo-3-thenoic acid[4] was dissolved in 200 cc. of ether. Then diazomethane was allowed to distil into the solution until the liquid became colored a deep yellow. Excess diazomethane was removed on the steam-bath. The remaining ethereal solution was fractionated and yielded 15 g. of methyl 2-bromo-3-thenoate, 93%, b.p. 114–115°/4 mm.

Anal. Calc'd for $C_6H_5BrO_2S$: C, 32.59; H, 2.28.
Found: C, 32.85; H, 2.45.

Methyl 3,3′-dithenate. In a three-neck flask fitted with a reflux condenser, a thermometer, and a mechanical stirrer was placed 3.4 g. of methyl 2-bromo-3-thenoate. The flask was heated in a silicone oil-bath[5] until the internal temperature reached 210° and then 4.6 g. of Baker's precipitated copper was added gradually during the course of one hour, while

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[3] All melting points were obtained with the Fisher-John apparatus.

[4] We are indebted to Dr. Carroll A. Hochwalt and Dr. O. J. Weinkauff of the Monsanto Chemical Company, St. Louis, Mo., for a generous supply of thiophene and 3-methylthiophene respectively.

[5] We wish to thank Mr. A. Kneitel of the General Electric Company, New York, N. Y. for a sample of the silicone oil used.

the temperature was maintained at 210–225°. When all of the copper was added, the temperature was raised to 250° for 15 minutes. After cooling, the solid mass was extracted with ether, and the ether removed on the steam-bath. The residual oil was dissolved in hot, dilute alcohol. Upon cooling 0.95 g. of yellow methyl 3,3′-dithenate (24%) deposited, m.p. 145–147°.

Anal. Calc'd for $C_{12}H_{10}O_4S_2$: C, 51.05; H, 3.57.
Found: C, 50.72; H, 3.49.

3,3′-Dithenic acid. Methyl 3,3′-dithenate (0.80 g.) was hydrolyzed by refluxing for four hours with 25 cc. of 10% potassium hydroxide. After cooling and acidification with hydrochloric acid, there was obtained 0.65 g. (90%) of a light yellow solid. The analytical sample was purified by vacuum sublimation, m.p. 175–185° d.

Anal. Calc'd for $C_{10}H_6O_4S_2$: C, 47.23; H, 2.38.
Found: C, 47.15; H, 2.31.

2-(6-Methyl-2-nitrophenyl)-3-thenoic acid. In the usual apparatus was placed 18.3 g. of 3-nitro-2-bromotoluene and 15.0 g. of methyl 2-bromo-3-thenoate. The flask was heated in an oil-bath until the internal temperature reached 230°. Then 17.70 g. of copper was added during the course of one hour, while the internal temperature was maintained at 230–240°. When all the copper had been added, the internal temperature was allowed to rise to 250° for 15 minutes. Upon cooling, the solid mass was thoroughly extracted with ether. After evaporation of the latter, the oily residue was saponified by refluxing for four hours with 100 cc. of 10% potassium hydroxide. The mixture was filtered, to remove some insoluble 2,2′-dimethyl-6,6′-dinitrobiphenyl, and the filtrate was carefully acidified with dilute hydrochloric acid. The black tar which was formed was dissolved in 200 cc. of benzene and boiled with Norit for 20 minutes. After filtration, the benzene solution was concentrated to half its volume and extracted with 100 cc. of 10% sodium hydroxide. Acidification of the alkaline solution with hydrochloric acid precipitated an orange-yellow solid which, after five recrystallizations from a mixture of benzene and petroleum ether, became light yellow and was analytically pure (9%), m.p. 183–186° with softening at 175°.

Anal. Calc'd for $C_{12}H_9NO_4S$: C, 54.74; H, 3.45.
Found: C, 54.54; H, 3.25.

Methyl 2-(6-methyl-2-nitrophenyl)-3-thenoate. This ester was obtained from the above acid with excess diazomethane in the manner described previously, m.p. 109–110° with softening at 100°.

Anal. Calc'd for $C_{13}H_{11}NO_4S$: C, 56.30; H, 3.99.
Found: C, 56.56; H, 3.85.

2-(6-Methyl-2-nitrophenyl)-3-thenamide. To 50 cc. of chloroform and 1.0 cc. of thionyl chloride was added 0.150 g. of 2-(6-methyl-2-nitrophenyl)-3-thenoic acid. The mixture was refluxed for three hours. After cooling, it was poured into a solution of 0.5 g. of sodium hydroxide in 12 cc. of ammonium hydroxide. The chloroform layer was separated and evaporated to dryness. The residual solid was dissolved in dilute alcohol and placed in the refrigerator. After four days, fine, yellow plates of the amide had deposited, m.p. 164–165° with softening at 150°.

Anal. Calc'd for $C_{12}H_{10}N_2O_3S$: C, 54.95; H, 3.84.
Found: C, 55.03; H, 3.48.

Resolution of 2-(6-methyl-2-nitrophenyl)-3-thenoic acid. Brucine (3.63 g.) and 2-(6-methyl-2-nitrophenyl)-3-thenoic acid (2.27 g.) were dissolved in 150 cc. of hot absolute alcohol and water, 2:1. The solution was placed in the freezing compartment of the refrigerator (*ca* −15°) and at the end of four days, 2.2 g. of a light yellow solid had deposited, m.p. 122–126°.

Rotation. Hydrated L-salt: 0.2150 g. made to 50 cc. with chloroform at 20° gave an initial α_D +0.522°, $l = 4$; $[\alpha]_D^{20}$ +30.35° and a final α_D −0.491°, $l = 4$; $[\alpha]_D^{20}$ −28.55° after 2.5 hours.

Anal. Calc'd for $C_{35}H_{35}N_3O_8S \cdot H_2O$: C, 62.21; H, 5.52.
Found: C, 62.17; H, 5.32.

L-*2-(6-Methyl-2-nitrophenyl)-3-thenoic acid.* The above brucine salt (1 g.) was shaken at

0° with 50 cc. of hydrochloric acid. At the end of two hours, the hydrochloric acid was decanted and another 50-cc. portion was added. The mixture was then placed in the refrigerator overnight. After filtration, the solid was washed with dilute hydrochloric acid until the washings gave a negative test for brucine, and then with water. It amounted to 0.25 g., m.p. 185–187° with softening at 170°.

Rotation. 0.2001 g. made to 50 cc. with methanol at 20° gave an initial α_D $-0.179°$, $l = 4$; $[\alpha]^{20}_D$ $-11.19°$ and a final α_D 0.000° after one hour.

Anal. Calc'd for $C_{12}H_9NO_4S$: C, 54.74; H, 3.45.
Found: C, 54.79; H, 3.25.

SUMMARY

1. The synthesis and resolution of a phenylthiophene exhibiting restricted rotation is reported.

2. The brucine salt which gave rise to an optically active acid mutarotated in solution.

3. The optically active acid racemized in solution.

4. A possible explanation for the discrepancies between the calculated and the observed optical stability is presented.

New York 58, N. Y.

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