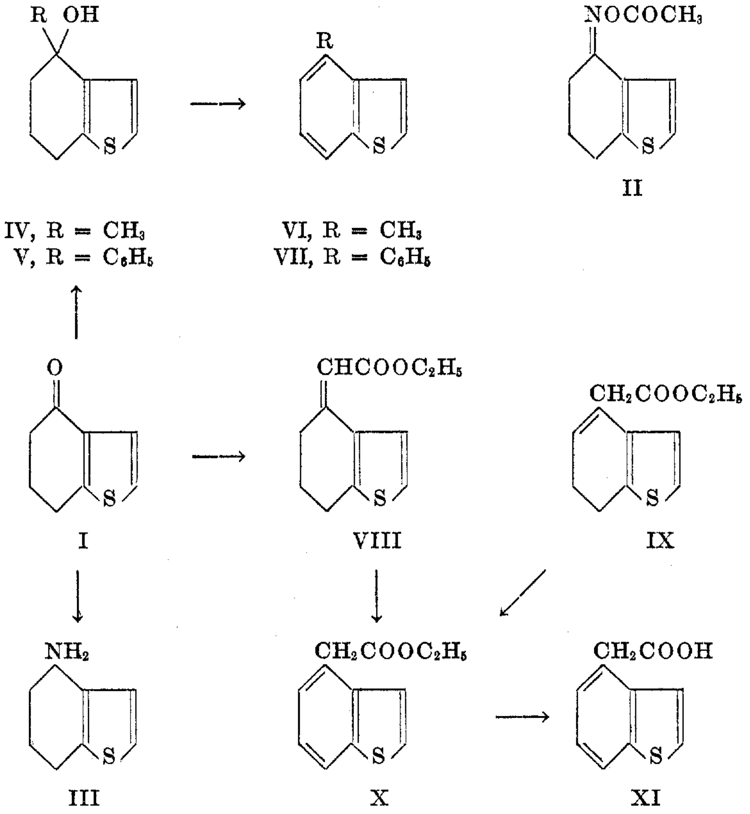
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

SYNTHESIS OF 4-SUBSTITUTED THIANAPHTHENE DERIVATIVES[1]

MILTON C. KLOETZEL, JESS E. LITTLE, JR., AND DAVID M. FRISCH

Received April 23, 1953

Among the many known derivatives of thianaphthene, those with a substituent in position 4 are relatively rare. Herein are described the syntheses of a number of 4-thianaphthenyl derivatives for which 4-keto-4,5,6,7-tetrahydrothianaphthene (I) proved to be a useful intermediate.



Cyclic ketone (I) was obtained by reduction of β-(2-thenoyl)propionic acid and subsequent cyclization of the resulting γ-(2-thienyl)butyric acid, through its acid chloride, according to the method of Fieser and Kennelly (1). β-(2-Thenoyl)propionic acid was best prepared (70% yield) through the reaction of thiophene with succinic anhydride (1) but was also obtained (18% yield) from the reaction of 2-thienylmagnesium iodide with succinic anhydride.

The cyclic ketone (I) formed an oxime which was converted to the corresponding acetate (II) by the action of acetic anhydride and anhydrous hydrogen

---

[1] Abstracted from the M.S. theses of Jess E. Little, Jr., and David M. Frisch.

chloride in benzene at room temperature. Hydrolysis of the acetate with warm 2 *N* sodium hydroxide regenerated the oxime.

4-Keto-4,5,6,7-tetrahydrothianaphthene (I) was successfully reduced to 4,5,6,7-tetrahydrothianaphthene with amalgamated zinc and refluxing hydrochloric acid, although the reaction was accompanied by some decomposition to produce hydrogen sulfide.

4-Amino-4,5,6,7-tetrahydrothianaphthene (III) was produced in 52% yield when cyclic ketone (I) was subjected to a modified (2) Leuckart reaction, and was characterized by formation of the crystalline acetyl and benzoyl derivatives. Dehydrogenation of the acetyl derivative with sulfur at 240° was unsuccessful.

Methylmagnesium iodide and phenylmagnesium bromide reacted smoothly with cyclic ketone (I) to give excellent yields of crystalline carbinols (IV and V). These were dehydrated and dehydrogenated, when heated with sulfur at 230–260°, to yield 4-methylthianaphthene (VI) and 4-phenylthianaphthene (VII) respectively. 4-Methylthianaphthene was readily characterized by conversion to its crystalline picrate.[2] 4-Phenylthianaphthene, like 1-phenylnaphthalene (3), failed to form complexes with picric acid or *sym*-trinitrobenzene and was therefore characterized by oxidation to the corresponding sulfone.

In the Reformatsky reaction with ethyl bromoacetate, the cyclic ketone (I) yielded a mixture of unsaturated esters (probably VIII and IX). Saponification of the mixture yielded two isomeric acids melting at 107–109° and 186–187° respectively. Dehydrogenation of the mixture of VIII and IX, followed by saponification, yielded a single compound, 4-thianaphtheneacetic acid (XI), which was easily converted to the corresponding sulfone.

As a plant growth-regulator, 4-thianaphtheneacetic acid (XI) has little or no formative activity (MOLARA < 200), as indicated by the leaf-repression test (4), but has very high auxin activity as measured in the hypocotyl curvature test (5).[3]

EXPERIMENTAL[4]

β-(2-Thenoyl)propionic acid was prepared from succinic anhydride by reaction with thiophene (1) or with 2-thienylmagnesium iodide. In the latter instance the procedure of Kitchen and Sandin (6) was followed except that succinic anhydride was employed instead of methylsuccinic anhydride; yield, 18% of colorless acid, m.p. 117.5–118.5°, which did not depress the m.p. of authentic acid (1).

The *oxime of 4-keto-4,5,6,7-tetrahydrothianaphthene* was prepared by adding sufficient ethanol to a mixture of 200 mg. of the cyclic ketone (I), 500 mg. of hydroxylamine hydrochloride, 3 ml. of water, and 2 ml. of 10% sodium hydroxide, to produce a clear solution and

---

[2] Greensfelder and Moore, U. S. Patent 2,478,914 (Aug. 16, 1949) claimed the catalytic production of 4-methylthianaphthene from 1-methyl-2-ethenylbenzene and hydrogen sulfide but reported no properties or characterization of this substance.

[3] We wish to thank Robert L. Weintraub, Chief, Chemical Branch, Chemical Corps Biological Laboratories, Camp Detrick, Frederick, Maryland, under whose direction these tests were conducted.

[4] Melting points are uncorrected. Analyses are by Dr. Adalbert Elek, Elek Micro Analytical Laboratories, Los Angeles; Dr. G. Oppenheimer, California Institute of Technology; Mr. Joseph Pirie, University of Southern California; and Mr. David M. Frisch.

then warming the solution on a steam-bath for 15 minutes. Upon cooling, 210 mg. (95% yield) of the oxime crystallized. One recrystallization from 40% ethanol yielded colorless crystals, m.p. 128–129°.

Anal. Calc'd for C_8H_9NOS: C, 57.45; H, 5.42.
Found: C, 57.61; H, 5.31.

The *oxime acetate* (II) was obtained when anhydrous hydrogen chloride was passed into a solution of 500 mg. of the aforementioned oxime and 0.4 ml. of acetic anhydride in 5 ml. of benzene at 25° for 2 hours and the solution was evaporated to dryness under reduced pressure; yield, 420 mg. (67%). Recrystallization from a mixture of ethanol and water yielded colorless needles, m.p. 133–134°.

Anal. Calc'd for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30.
Found: C, 57.14; H, 5.23.

A mixture of 100 mg. of the oxime acetate, 2 ml. of 95% ethanol, 5 ml. of water, and 2 ml. of 2 *N* sodium hydroxide was heated for 15 minutes, diluted with 4 ml. of water, and acidified with solid carbon dioxide. Recrystallization of the precipitate from dilute ethanol yielded colorless crystals, m.p. 127–128°, which did not depress the m.p. of the oxime.

4,5,6,7-Tetrahydrothianaphthene. To 52 g. of granulated zinc, amalgamated in the customary manner (7), was added 100 ml. of 18% hydrochloric acid and then 6.5 g. of 4-keto-4,5,6,7-tetrahydrothianaphthene (1). An additional 20-ml. portion of 18% hydrochloric acid was added each hour during a 6.5-hour reflux period. Hydrogen sulfide was slowly evolved. The dried benzene extract of the cooled reaction mixture was distilled under reduced pressure and yielded 3.5 g. (59%) of colorless 4,5,6,7-tetrahydrothianaphthene, b.p. 53–58° at 3 mm. (8).

Anal. Calc'd for $C_8H_{10}S$: C, 69.51; H, 7.29.
Found: C, 69.72; H, 7.51.

4-Amino-4,5,6,7-tetrahydrothianaphthene (III). Formamide (16 g.) was placed in a distilling flask and heated slowly to 165°. At this temperature 10 g. of 4-keto-4,5,6,7-tetrahydrothianaphthene was added and the mixture was heated to 165–185° until no more ammonium carbonate was deposited in the side arm of the flask (3–5 hours). Water and ketone which distilled during the period of heating were collected in a separatory-funnel and the ketone was returned to the reacting mixture. The cooled reaction mixture was diluted with twice its volume of water and was shaken vigorously, whereupon 9.0 g. (76%) of 4-formylamino-4,5,6,7-tetrahydrothianaphthene solidified. This crude material was hydrolyzed by heating gently for 4 hours with 60 ml. of 10% hydrochloric acid. The cooled solution was made alkaline with 10% sodium hydroxide and the precipitated oil was separated from the aqueous phase with the aid of ether. Distillation of the dried ether extract under reduced pressure yielded 5.2 g. (52% based on ketone) of colorless 4-amino-4,5,6,7-tetrahydrothianaphthene, b.p. 74–78° at 2 mm.

Anal. Calc'd for $C_8H_{11}NS$: C, 62.70; H, 7.23.
Found: C, 62.87; H, 7.22.

The *4-acetylamino-4,5,6,7-tetrahydrothianaphthene* which precipitated when 1 g. of the amine (III) was heated for a few minutes with three times its volume of acetic anhydride and then poured into 40 ml. of water was recrystallized from 20% ethanol; yield, 1.02 g. (80%), m.p. 168–169°.

Anal. Calc'd for $C_{10}H_{13}NOS$: C, 61.50; H, 6.71; S, 16.42.
Found: C, 61.80; H, 6.79; S, 16.15.

When 100 mg. of 4-acetylamino-4,5,6,7-tetrahydrothianaphthene was heated to 240° for 20 minutes with 33 mg. of sulfur there was produced a brown tar from which no crystalline material could be extracted with diluted ethanol.

4-Benzoylamino-4,5,6,7-tetrahydrothianaphthene was prepared by shaking a mixture of 1 ml. of the amine (III), 3 ml. of water, 1 ml. of benzoyl chloride, and 5 ml. of 10% sodium hydroxide and recrystallizing the precipitate from dilute ethanol; m.p. 123.5–124.5°.

Anal. Calc'd for $C_{15}H_{15}NOS$: C, 70.00; H, 5.87; N, 5.44; S, 12.46.
Found: C, 70.22; H, 6.02; N, 5.54; S, 12.06.

4-Hydroxy-4-methyl-4,5,6,7-tetrahydrothianaphthene (IV). When a solution of 7 g. of the cyclic ketone (I) in 35 ml. of anhydrous ether was added dropwise at room temperature to the mechanically-stirred Grignard reagent prepared from 9 g. of methyl iodide, 1.5 g. of magnesium, and 30 ml. of ether, a colorless complex separated immediately. The mixture was chilled and hydrolyzed with 11 ml. of saturated ammonium chloride solution. Evaporation of the filtered ether layer at room temperature yielded 7 g. (91%) of carbinol IV, m.p. 68–73°. Recrystallization from Skellysolve B yielded colorless cubes, m.p. 75–76°, which gave a deep red color with concentrated sulfuric acid.

Anal. Calc'd for $C_9H_{12}OS$: C, 64.24; H, 7.19.
Found: C, 64.06; H, 7.59.

4-Methylthianaphthene (VI). A mixture of 3.8 g. of carbinol IV and 0.72 g. of sulfur was heated in an eight-inch test tube. Steam was evolved at 150° followed by hydrogen sulfide as the temperature was raised to 230° for 20 minutes. Reaction was completed by elevating the temperature to 250° for 10 minutes. Distillation of the residue under reduced pressure yielded 2.7 g. (81%) of colorless 4-methylthianaphthene boiling at 55–57° at 3 mm. and melting between −6° and −4°.

Anal. Calc'd for C_9H_8S: S, 21.63. Found: S, 21.60.

Addition of 4-methylthianaphthene to a hot saturated solution of picric acid in ethanol yielded, upon cooling, the *picrate* in orange needles, m.p. 135–136°.

Anal. Calc'd for $C_{15}H_{11}N_3O_7S$: C, 47.74; H, 2.94.
Found: C, 47.62; H, 3.01.

4-Hydroxy-4-phenyl-4,5,6,7-tetrahydrothianaphthene (V) was prepared from 8 g. of the cyclic ketone (I), 16 g. of bromobenzene, and 2.5 g. of magnesium, in the manner previously described for the methyl analog. After standing at 0° for 21 hours, the reaction mixture was hydrolyzed with 19 ml. of saturated ammonium chloride solution. Evaporation of the ether layer yielded 10.8 g. (89%) of crude carbinol, m.p. 45–54°. Recrystallization from Skellysolve F produced colorless needles, m.p. 65–67°. With concentrated sulfuric acid this carbinol gave an amber color.

Anal. Calc'd for $C_{14}H_{14}OS$: C, 73.00; H, 6.13; S, 13.91.
Found: C, 73.28; H, 6.20; S, 13.50.

4-Phenylthianaphthene (VII) was obtained by dehydration and dehydrogenation of carbinol V in the manner described for the methyl analog; b.p. 125–127° at 3 mm.; yield, 82%. Recrystallization from 95% ethanol or from Skellysolve F afforded pure, colorless material, m.p. 46–47°.

Anal. Calc'd for $C_{14}H_{10}S$: C, 79.96; H, 4.79.
Found: C, 79.24; H, 4.67.

Since 4-phenylthianaphthene would not form a picrate in absolute ethanol or a *sym*-trinitrobenzene derivative in methanol, it was characterized by oxidation to the corresponding sulfone. 4-Phenylthianaphthene (500 mg.) slowly dissolved as it was refluxed for 1 hour with a mixture of 3 ml. of glacial acetic acid and 2.5 ml. of 30% hydrogen peroxide. When the resulting solution was diluted with 10 ml. of water and cooled to 5°, 460 mg. (80%) of 4-phenylthianaphthene-1-dioxide crystallized. Recrystallization from dilute ethanol yielded pure sulfone in colorless needles, m.p. 139°.

Anal. Calc'd for $C_{14}H_{10}O_2S$: C, 69.39; H, 4.16.
Found: C, 69.27; H, 4.32.

Reformatsky reaction of 4-keto-4,5,6,7-tetrahydrothianaphthene with ethyl bromoacetate. To a hot mixture of 48 g. of amalgamated zinc, 12 ml. of ethyl bromoacetate, 400 mg. of iodine, 200 ml. of dry benzene, and 200 ml. of dry ether, was added 16 g. of cyclic ketone (I). While the mixture was refluxed for 2 hours, 48 g. of amalgamated zinc and 400 mg. of iodine were added at each half-hour interval. Finally 12 ml. of ethyl bromoacetate was added and the mixture was refluxed for an additional period of 2.5 hours. The cooled mixture was decomposed with cold 10% hydrochloric acid and the organic layer, combined with two benzene extracts of the aqueous layer, was washed with dilute ammonia water and finally distilled under reduced pressure. A mixture of isomeric esters (VIII and IX) distilled at 135–150° at 3 mm.; yield, 17 g. (73%).

Anal. Calc'd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.34.
Found: C, 64.60; H, 6.46.

A 2-g. sample of the mixture of esters VIII and IX was heated with 50 ml. of 20% sodium hydroxide solution until the organic layer disappeared and the solution was then acidified with hydrochloric acid. The precipitated acids were extracted with ether. Evaporation of the ether and recrystallization of the residue from glacial acetic acid yielded 1.4 g. (80%) of colorless acid, m.p. 186–187°.

Anal. Calc'd for $C_{10}H_{10}O_2S$: C, 61.82; H, 5.19.
Found: C, 61.79; H, 5.22.

Dilution of the acetic acid mother liquor with water deposited 200 mg. (11%) of an isomeric acid in colorless needles, m.p. 107–109°.

Anal. Calc'd for $C_{10}H_{10}O_2S$: C, 61.82; H, 5.19.
Found: C, 61.81; H, 5.35.

4-Thianaphtheneacetic acid (XI). A solution of 12 g. of mixed esters VIII and IX and 14.5 g. of chloranil in 100 ml. of xylene was refluxed for 36 hours. The cooled solution was filtered and distilled under reduced pressure to yield 6.5 g. (55%) of *ethyl 4-thianaphthene-acetate* (*X*), b.p. 130° at 3 mm. Saponification and acidification as previously described yielded 4.1 g. (72%) of 4-thianaphtheneacetic acid which crystallized from water in colorless needles, m.p. 146–146.5°.

Anal. Calc'd for $C_{10}H_8O_2S$: C, 62.47; H, 4.19.
Found: C, 62.45; H, 4.35.

A mixture of 500 mg. of 4-thianaphtheneacetic acid, 3 ml. of glacial acetic acid, and 2.5 ml. of 30% hydrogen peroxide was refluxed for 15 minutes and then evaporated to dryness. Crystallization of the residue from water yielded 400 mg. (70%) of the colorless *sulfone of 4-thianaphtheneacetic acid*, m.p. 181°.

Anal. Calc'd for $C_{10}H_8O_4S$: C, 53.56; H, 3.59.
Found: C, 53.35; H, 3.84.

SUMMARY

4-Keto-4,5,6,7-tetrahydrothianaphthene has been employed for the synthesis of several 4-substituted thianaphthene derivatives. Clemmensen reduction yielded 4,5,6,7-tetrahydrothianaphthene. 4-Amino-4,5,6,7-tetrahydrothianaphthene was obtained through a Leuckart reaction. The cyclic ketone reacted with appropriate Grignard reagents to produce tertiary carbinols which were dehydrated and subsequently dehydrogenated to 4-methylthianaphthene and 4-phenylthianaphthene respectively. 4-Thianaphtheneacetic acid, prepared from the cyclic ketone *via* the Reformatsky reaction, was shown to have very high auxin activity as measured in the hypocotyl curvature test.

LOS ANGELES 7, CALIFORNIA

REFERENCES

(1) FIESER AND KENNELLY, *J. Am. Chem. Soc.*, **57**, 1611 (1935).
(2) INGERSOLL, BROWN, KIM, BEAUCHAMP, AND JENNINGS, *J. Am. Chem. Soc.*, **58**, 1808 (1936).
(3) ORCHIN AND REGGEL, *J. Am. Chem. Soc.*, **69**, 505 (1947).
(4) BROWN AND WEINTRAUB, *Botan. Gaz.*, **111**, 448 (1950).
(5) WEINTRAUB, BROWN, THRONE, AND YEATMAN, *Am. J. Botany*, **38**, 435 (1951).
(6) KITCHEN AND SANDIN, *J. Am. Chem. Soc.*, **67**, 1645 (1945).
(7) MARTIN, *J. Am. Chem. Soc.*, **58**, 1438 (1936).
(8) CAGNIANT, *Compt. rend.*, **230**, 100 (1950).