m.p. 223–225°. The compound is very soluble in water and moderately soluble in neutral dioxane.

Anal. Calcd. for $C_{16}H_{24}O_{10}NCl$ (425.82): C, 45.13; H, 5.68; N, 3.29. Found: C, 45.18; H, 5.77; N, 3.26.

Periodate Oxidation.—Measured quantities (0.005 mmole) of the two free inosamines were treated with 7.65 molar equivalents of sodium metaperiodate heavily buffered with sodium bicarbonate. The rates of periodate consumption are plotted in Fig. 3.

Acyl Migration.—Two-millimole samples of the N-acetyl derivatives were dissolved in 25 ml. of *N* hydrochloric acid. The solutions were maintained at 30 ± 0.5° in glass stoppered flasks and analyzed periodically for free amino groups by the Van Slyke method. The results are plotted in Fig. 4. Control samples of the free amines gave the theoretical quantities of nitrogen in the Van Slyke apparatus.

MADISON 6, WISCONSIN

[CONTRIBUTION FROM THE AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

Thianaphtheno[3,2-c]pyridine and Certain Derivatives

BY DAVID B. CAPPS[1] AND CLIFF S. HAMILTON

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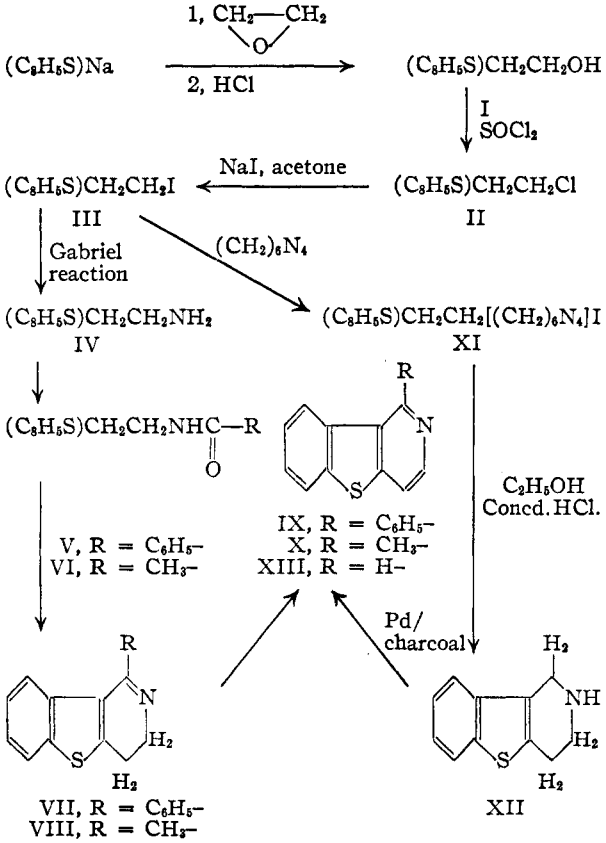
2-Thianaphthenyl sodium was treated with ethylene oxide, giving 2-thianaphthene-ethanol. The alcohol was converted to its chloro analog and the latter to the iodo compound, which gave 2-thianaphthene-ethylamine by Gabriel's phthalimide reaction. 2-Thianaphthene-ethylamine was benzoylated and acetylated yielding amides which were converted to the corresponding dihydroisoquinoline-like compounds by the Bischler–Napieralski reaction. These amines were then aromatized giving 1-phenyl- and 1-methylthianaphtheno[3,2-c]pyridine. 2-(2-Iodoethyl)-thianaphthene formed an addition compound with hexamethylenetetramine which gave 1,2,3,4-tetrahydrothianaphtheno[3,2-c]pyridine upon alcoholysis in acid, instead of the expected primary amine. Dehydrogenation of this base provided thianaphtheno[3,2-c]pyridine.

Several simple 2-position derivatives of thianaphthene have not been reported. Therefore, it was of interest to synthesize 2-thianaphthene-ethanol and from it, derivatives leading to thianaphtheno[3,2-c]pyridines. The accompanying diagram illustrates the method of synthesis.



2-Thianaphthenyl sodium[2] gave 2-thianaphthene-ethanol (I) on treatment with ethylene oxide. The alcohol was converted to 2-(2-chloroethyl)-thianaphthene (II), and the latter to 2-(2-iodoethyl)-thianaphthene[3] (III). The iodide proved to be the better halide for use in Gabriel's phthalimide reaction.[4] The intermediate substituted phthalimide was hydrolyzed by a modification[5] of Ing and Manske's[6] hydrazine hydrolysis. Benzoylation and acetylation of 2-thianaphthene-ethylamine gave amides (V and VI) which underwent the Bischler–Napieralski reaction[7a] giving 1-phenyl- and 1-methyl-3,4-dihydrothianaphtheno[3,2-c]pyridine (VII and VIII). The ring closures were effected both by using phosphorus pentoxide at elevated temperatures and phosphorus pentachloride at room temperature.[8] Attempts to cyclize the benzamide (V) using phosphorus pentoxide suspended in hot xylene failed until glass balls were introduced into the stirred reaction mixture to prevent the deposit of the phosphate salt of the basic product, insoluble in xylene, on the suspended particles of phosphorus pentoxide.

When phosphorus oxychloride in boiling xylene was used to effect ring closure of the benzamide derivative, the fully aromatized product (IX) was obtained, not the dihydro derivative (VII) which ample precedent[7a] would lead one to expect.

1-Phenyl-3,4-dihydrothianaphtheno[3,2-c]pyridine (VII) was aromatized by heating its xylene solution under reflux in the presence of activated carbon (Nuchar). The methyl analog was dehydrogenated in the presence of palladized charcoal.

Attempts were made to prepare 2-thianaphthene-ethylamine by the Delépine reaction.[9] Treatment of the addition compound (XI) of hexamethylenetetramine and 2-(2-iodoethyl)-thianaphthene

(1) Parke, Davis and Company Fellow.

(2) A. Schönberg, E. Petersen and H. Kaltschmitt, *Ber.*, **66**, 233 (1933).

(3) Procedure patterned after that of F. F. Blicke and J. H. Burckhalter, THIS JOURNAL, **64**, 480 (1942), for 3-(α-thienyl)-propyl iodide.

(4) S. Gabriel, *Ber.*, **20**, 2224 (1887).

(5) H. J. Barber and W. R. Wragg, *J. Chem. Soc.*, 1331 (1947).

(6) H. R. Ing and R. H. F. Manske, *ibid.*, 2348 (1926).

(7) (a) R. Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 74; (b) p. 151.

(8) J. M. Gulland and R. D. Haworth, *J. Chem. Soc.*, 581 (1928).

(9) Delépine, *Bull. soc. chim. France*, **13**, 358 (1895).

with ethanol and hydrochloric acid[10] yielded 1,2,3,4-tetrahydrothianaphtheno[3,2-c]pyridine (XII) in 78% yield, rather than the expected primary amine. The production of this cyclic amine may be easily explained. In the alcoholysis of the addition compound, six equivalents of formaldehyde diethylacetal are formed. This acetal, with suitably activated β-arylethylamines in the presence of mineral acids, undergoes the Pictet–Spengler reaction[7b] to yield tetrahydroisoquinoline-like bases. The tetrahydroamine was smoothly dehydrogenated to thianaphtheno[3,2-c]pyridine (XIII) by heating in the presence of palladized charcoal.[11]

Experimental[12]

2-Thianaphthene-ethanol (I).—2-Thianaphthenylsodium[2] was prepared by heating under reflux a stirred mixture of 120 g. (0.9 mole) of thianaphthene, 100 g. (4.35 mole) of powdered sodium and 3.5 l. of dry ether for 45 hours. Anhydrous conditions were maintained. The resulting mixture was cooled to 5° under dry nitrogen and 400 ml. of 4 *M* ethylene oxide in ether added over 1 hour. The mixture was stirred an additional hour without the cooling bath and the suspended sodium alcoholate decanted from the unreacted sodium. The ethereal suspension was shaken with about one-fourth its volume of water containing enough hydrochloric acid to render that phase acidic to Congo red paper. The ether layer was washed with water and dried over magnesium sulfate.

The residue remaining after concentrating the ethereal solution was distilled, providing 2 g. of unreacted thianaphthene and 78 g. of crude 2-thianaphthene-ethanol, b.p. 171–186° (4.5–6 mm.). Recrystallization from benzene–petroleum ether gave 67.2 g. (43%) of lustrous white leaflets, m.p. 76–79.5°. The analytical sample melted at 79.5–80.5°.

Anal. Calcd. for $C_{10}H_{10}OS$: C, 67.38; H, 5.66. Found: C, 67.37; H, 5.72.

2-(2-Chloroethyl)-thianaphthene (II).—I (33.2 g., 0.186 mole) was placed in a 250-ml. Claisen flask fitted with a dropping funnel and a reflux condenser. The side arm of the flask was stoppered. Thionyl chloride (28.8 g., 0.242 mole) was added to the alcohol over 45 minutes at room temperature. The resulting mixture was heated in an oil-bath the temperature of which was held at 135–40° for 20 minutes. The reaction flask was then fitted with an ebulliator and a thermometer and the product distilled under reduced pressure. The slightly yellow oil weighed 31.4 g. (86%), b.p. 148–164° (6–10 mm.). An analytical sample was obtained by careful redistillation through a Vigreux column; b.p. 148.5° (6 mm.), $n^{25}D$ 1.6235.

Anal. Calcd. for $C_{10}H_9SCl$: C, 61.06; H, 4.61. Found: C, 61.01; H, 4.67.

2-(2-Iodoethyl)-thianaphthene (III).—A mixture consisting of 57.3 g. (0.291 mole) of II, 89 g. (0.594 mole) of sodium iodide and 250 ml. of dry acetone was stirred under gentle reflux for 9 hours. The mixture was cooled and filtered. The filtrate was freed of acetone by evaporation under reduced pressure and the residue extracted with a total of 600 ml. of hot benzene in several portions. The benzene extracts were combined and concentrated under reduced pressure, leaving a brown oil which was crystallized from absolute ethanol, providing 73.4 g. (87.5%) of lustrous white leaflets, m.p. 66–68.5°. A purified sample melted at 69–70°.

Anal. Calcd. for $C_{10}H_9SI$: C, 41.68; H, 3.15. Found: C, 41.66; H, 3.25.

N-[2-(2-Thianaphthenyl)-ethyl]-phthalimide.—An intimate mixture of 47 g. (0.163 mole) of III and 34 g. (0.1835 mole) of potassium phthalimide was heated at 167° for 9 hours in an atmosphere of nitrogen. This temperature was maintained by jacketing the reaction vessel with a bath of refluxing phenetole. The resulting mixture was extracted with 300 ml. of chloroform and the extract washed with dilute sodium hydroxide to remove phthalimide. The chloroform solution was then washed with water, dried over magnesium sulfate and evaporated under reduced pressure. The residual oily solid was washed with cold ether and recrystallized from toluene, providing 28 g. (56%) of the substituted phthalimide, m.p. 162–65°. The analytical sample melted at 165–66°; rods from ethyl acetate.

Anal. Calcd. for $C_{18}H_{13}O_2NS$: C, 70.33; H, 4.26; N, 4.56. Found: C, 70.41; H, 4.45; N, 4.45.

2-Thianaphthene-ethylamine (IV).—A solution of 43.2 g. (0.1405 mole) of N-[2-(2-thianaphthenyl)-ethyl]-phthalimide and 16 g. (0.32 mole) of hydrazine hydrate in 425 ml. of chloroform and 240 ml. of absolute ethanol was allowed to stand at room temperature for 4 days. The gel was broken up and the volatiles removed at room temperature under reduced pressure.

The residue was shaken for 2 hours with a mixture of 480 ml. of chloroform, 220 ml. of 2 *N* ammonium hydroxide and 300 ml. of water. The layers were separated and the aqueous one further extracted with 250 ml. of chloroform in several portions. The combined chloroform solutions were then extracted with 250 ml. of normal acetic acid in 5 portions. The combined acetic acid extracts were basified with excess concentrated ammonium hydroxide and the resulting mixture extracted with 275 ml. of ether in several small portions. These extracts were combined, dried over potassium hydroxide pellets, concentrated and distilled under reduced pressure providing 20.1 g. (81%) of IV, b.p. 164–67.5° (11.5 mm.). This amine readily absorbed carbon dioxide from the atmosphere and was inconvenient to handle in the free state. For analytical purposes its hydrochloride was prepared, crystallizing as platelets out of methanol, m.p. 286–290° (dec.).

Anal. Calcd. for $C_{10}H_{12}NSCl$: C, 56.18; H, 5.66; N, 6.55. Found: C, 56.15; H, 5.72; N, 6.57.

N-Benzoyl-2-thianaphthene-ethylamine (V).—A sample of IV, the unpurified product of the hydrazine hydrolysis of 0.0319 mole of N-[2-(2-thianaphthenyl)-ethyl]-phthalimide, was dissolved in 15 ml. of pyridine, cooled in ice and treated dropwise with 4.8 ml. (5.85 g. or 0.0417 mole) of benzoyl chloride. The resulting mixture was allowed to stand in ice for 1.5 hours, then warmed on a steam-bath to effect complete solution and poured into 100 ml. of ice-water. The suspension was treated with excess sodium carbonate, diluted to 200 ml. and filtered. The crude amide was recrystallized from benzene, providing 6.2 g. of V, m.p. 152–154.5°. The yield represented an over-all yield of 69% for the hydrazine hydrolysis and benzoylation. The analytical sample melted at 153–154.5°.

Anal. Calcd. for $C_{17}H_{15}ONS$: C, 72.56; H, 5.37; N, 4.98. Found: C, 72.72; H, 5.51; N, 4.83.

N-Acetyl-2-thianaphthene-ethylamine (VI).—To 8.4 g. (0.0475 mole) of IV was added 10 ml. of glacial acetic acid dropwise and with cooling. To this mixture was added 6.3 ml. (0.0665 mole) of acetic anhydride all at once. The resulting yellow solution was allowed to stand 40 hours at room temperature and treated with 0.5 ml. of water and a drop of sodium hydroxide. After standing 6 hours at room temperature the solution was poured into 200 ml. of cold water with stirring. The suspension was cooled and the precipitate collected at the pump. Recrystallized from benzene and petroleum ether, the product weighed 10.1 g. (97%), m.p. 119.5–121°. Analytical sample melted at 120–121°.

Anal. Calcd. for $C_{12}H_{13}ONS$: C, 65.72; H, 5.98; N, 6.39. Found: C, 65.44; H, 6.01; N, 6.17.

1-Phenyl-3,4-dihydrothianaphtheno[3,2-c]pyridine (VII). **a.**—A mixture of 6.45 g. (0.023 mole) of V, 13 g. of phosphorus pentoxide, 100 ml. of xylene and 30 ml. of glass balls (approx. 3 mm. diameter) was stirred for 7 hours on a steam-bath. Anhydrous conditions were maintained. The resulting mixture was shaken with 300 ml. of benzene and 300 ml. of water. The yellow aqueous layer was basified with sodium hydroxide and extracted with ether. The dried ether solution yielded 5.1 g. (87%) of the hydrochloride salt of VII on treatment with dry hydrogen chloride. The free base, 4.27 g. (83%), m.p. 113.5–18° (dec.), was obtained by treating the salt, in methanol, with concd. sodium hydroxide. The analytical sample melted at 121–122° (dec.) from aqueous methanol.

(10) M. Heidelberger, "An Advanced Laboratory Manual of Organic Chemistry," The Chemical Catalog Co. (Reinhold Publ. Corp.), New York, N. Y., 1923, p. 26.

(11) E. Späth and E. Lederer, *Ber.*, **63**, 2102 (1930).

(12) All melting points are uncorrected.

Anal. Calcd. for $C_{17}H_{13}NS$: C, 77.53; H, 4.97; N, 5.32. Found: C, 77.60; H, 5.19; N, 5.37.

This compound was sensitive to heat and somewhat so to air, being particularly vulnerable when in solution. Only gentle warming could be employed when recrystallizing it, and this for only a short time, otherwise a product of lower melting point was obtained, presumably due to a tendency to lose hydrogen.

b.—One gram (0.00356 mole) of V was added portionwise to a cold suspension of 0.73 g. (0.0036 mole) of phosphorus pentachloride in 6 ml. of chloroform. The resulting clear yellow solution was allowed to stand 2 days at room temperature, then evaporated under reduced pressure. The residue was dissolved in 50 ml. warm water, filtered, and basified with excess ammonium hydroxide, providing a white precipitate of crude VII. Recrystallization from petroleum ether provided 0.73 g. (78%), m.p. 118.5–121° (dec.).

1-Methyl-3,4-dihydrothianaphtheno[3,2-c]pyridine (VIII).—To a cold suspension of 8.6 g. (0.0413 mole) of phosphorus pentachloride and 40 ml. of chloroform was added 4.3 g. (0.0196 mole) of VI portionwise. A voluminous yellow precipitate formed rapidly, accompanied by the evolution of hydrogen chloride. The mixture was allowed to stand at room temperature overnight, evaporated under reduced pressure and the residue was sifted into 150 ml. of cold water. The resulting yellow solution was filtered and basified with potassium hydroxide, precipitating an amber oil which completely solidified after two days in the refrigerator, giving 3.92 g. of crude VIII. Recrystallization from petroleum ether gave 2.55 g., m.p. 59.5–61.5°. A second crop of 0.91 g., m.p. 58–61°, brought the yield to 88%.

The hydrochloride was prepared for analytical purposes, m.p. 200–206° (dec.), darkening at 180°.

Anal. Calcd. for $C_{12}H_{12}NSCl$: C, 60.62; H, 5.09; N, 5.89. Found: C, 60.43; H, 5.29; N, 5.86.

1-Phenylthianaphtheno[3,2-c]pyridine (IX). a.—A mixture of 0.73 g. of VII, 2 g. of activated carbon (Nuchar) and 35 ml. of xylene was heated under reflux for 14.5 hours. The suspension was filtered and the filtrate found to contain 0.48 g. (67%) of IX, m.p. 123.5–124.5°, out of aqueous methanol. A mixture of this with VII melted from below 88 to 91°. A mixture with IX, prepared by heating VII with palladized charcoal in the absence of solvent,[11] melted without depression.

Anal. Calcd. for $C_{17}H_{11}NS$: C, 78.13; H, 4.24; N, 5.36. Found: C, 78.24; H, 4.25; N, 5.37.

b.—A mixture of 1.00 g. of V, 4 ml. of phosphorus oxychloride and 8 ml. of dry xylene was heated at 110–120° for 2 hours, then at reflux temperature for 10.5 hours. The excess oxychloride and some xylene were removed under reduced pressure and the residue treated with 80 ml. of hot water containing a little hydrochloric acid. The aqueous layer was filtered, cooled, basified with ammonium hydroxide and extracted with ether. Evaporation of the ether left an oil which was crystallized from petroleum ether, providing 0.60 g. of IX, m.p. 123–124.5°. A second crop, 0.06 g., m.p 122–124°, raised the yield to 71%. A mixture of this with the analyzed sample of IX melted without depression.

1-Methylthianaphtheno[3,2-c]pyridine (X).—A mixture of 2.90 g. of VIII, 2.0 g. of palladized charcoal and 40 ml. of xylene was heated under reflux for 4.5 hours. The mixture was filtered and the catalyst extracted with benzene in a Soxhlet apparatus. This extract was combined with the xylene filtrate and the resulting solution evaporated. The oil remaining was triturated with 9 ml. of warm petroleum ether and this extract decanted. Cooling precipitated crude X. Recrystallization from petroleum ether gave 1.45 g., m.p. 77.5–81°. A second crop of 0.20 g., m.p. 77–80.5°, brought the yield to 57.5%. The analytical sample melted at 81–83°.

Anal. Calcd. for $C_{12}H_9NS$: C, 72.33; H, 4.55; N, 7.03. Found: C, 72.13; H, 4.66; N, 6.91.

Addition Compound of Hexamethylenetetramine and 2-(2-Iodoethyl)-thianaphthene (XI).—A solution of 1.44 g. (0.005 mole) of III and 1.75 g. (0.0125 mole) of hexamethylenetetramine in 15 ml. of dry chloroform was allowed to stand in the dark at room temperature for 71 days. The precipitated addition compound was collected on a filter, washed with chloroform and dried, providing 2.06 g. (96%) of white leaflets decomposing at 154–159°.

Anal. Calcd. for $C_{16}H_{21}N_4SI$: N, 13.08. Found: N, 13.31.

1,2,3,4-Tetrahydrothianaphtheno[3,2-c]pyridine (XII).—A mixture of 25.2 g. (0.059 mole) of XI, 16 ml. (0.192 mole) of concd. hydrochloric acid and 70 ml. of 95% ethanol was stirred for 36 hours at room temperature, then allowed to stand unstirred for 36 hours longer. The brown mixture was heated under reflux for 15 minutes, then the condenser arranged for distillation and 64 ml. of distillate collected. To the residue was added 10 ml. of concd. hydrochloric acid and 40 ml. of absolute ethanol, refluxed 60 minutes, then 45 ml. of distillate taken off. The residue was triturated with 300 ml. of water and 150 ml. of benzene. The two-phase mixture was cooled to 0°, precipitating the hydroiodide of XII in the aqueous layer. The salt was collected on a filter and the phases of the filtrate separated. The aqueous phase was evaporated to half volume on a steam-bath and transferred, along with the salt, to a separatory funnel where the suspension was basified with potassium hydroxide and extracted with ether. The dried extracts were concentrated and distilled under reduced pressure, providing 8.70 g. (78%) of XII as a clear viscous yellow-green oil, b.p. 167–165° (5–4 mm.). The hydrochloride was prepared for analytical purposes, needles from 95% ethanol, m.p. 250–256° (partial decomposition).

Anal. Calcd. for $C_{11}H_{12}NSCl$: C, 58.52; H, 5.36; N, 6.21. Found: C, 58.47; H, 5.48; N, 6.21.

The benzoyl derivative, m.p. 128.5–131.5° (dec.), was prepared by treating the amine in pyridine with benzoyl chloride.

Anal. Calcd. for $C_{18}H_{15}ONS$: C, 73.69; H, 5.15; N, 4.78. Found: C, 73.79; H, 5.32; N, 4.78.

Thianaphtheno[3,2-c]pyridine (XIII).—A mixture of 3.15 g. of XII and 4.0 g. of palladized charcoal, in an atmosphere of nitrogen, was heated to 200° over 20 minutes, held at 200° for 75 minutes, then heated to 230° over 20 minutes. The charge was cooled and extracted with acetone in a soxhlet apparatus. The extract was filtered through Celite and evaporated. The solid residue was extracted with 20 ml. of petroleum ether at 35°, and decanted from the undissolved oil. Cooling the decantate precipitated 1.92 g. of XIII, m.p. 67–70°. A second crop, m.p. 65–68°, weighed 0.21 g.; total yield 2.13 g. (69%). The analytical sample, white needles from petroleum ether, melted at 69–70.5°.

Anal. Calcd. for $C_{11}H_7NS$: C, 71.32; H, 3.81; N, 7.56. Found: C, 71.33; H, 3.77; N, 7.50.

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LINCOLN 8, NEBRASKA