[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

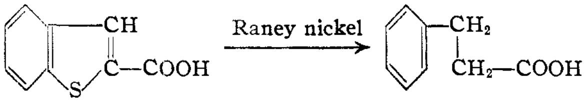
Derivatives of Thianaphthene. I[1]

BY F. F. BLICKE AND DON G. SHEETS[2]

This paper deals with the synthesis of 3-chloromethylthianaphthene, thianaphthene-2- and thianaphthene-3-acetic acid and certain derivatives which were prepared from them.

We have found that thianaphthene can be chloromethylated very readily.[3] Since conversion of the chloromethyl into the cyanomethyl derivative and hydrolysis of the latter substance yielded a thianaphthene-acetic acid (m. p. 108–109°) which melted at the same temperature as the thianaphthene-3-acetic acid (m. p. 109°) described by Crook and Davies,[4] chloromethylation of thianaphthene must produce the 3-chloromethyl derivative as would be expected. Furthermore, we have prepared an acid (m. p. 141–142°) which must be thianaphthene-2-acetic acid since it was obtained from thianaphthene-2-carboxylic acid, the structure of which has been established,[5] by the Arndt–Eistert reaction.

It was discovered that the structures of several thianaphthene carboxylic acids can be determined by a very simple, direct procedure. Thus when thianaphthene-2-carboxylic acid was heated at 75° for a short time with Raney nickel, in sodium carbonate solution, β-phenylpropionic acid was obtained in 93% yield. γ-Phenylbutyric acid was formed, in good yield, from thianaphthene-2-acetic acid, and thianaphthene-3-acetic acid was converted into β-phenylbutyric acid. A study of the general applicability of this process for a variety of thiophene and thianaphthene derivatives is in progress.[6]



2-(3-Thianaphthenylmethyl)-imidazoline was prepared by interaction of thianaphthene-3-acetic acid, ethylenediamine dihydrochloride and ethylenediamine, and also from 3-thianaphthenylacetimino ethyl ether hydrochloride and ethylenediamine. 2-(2-Thianaphthenylmethyl)-imidazoline was obtained when a mixture of thianaphthene-2-acetic acid, ethylenediamine dihydrochloride and ethylenediamine was heated, and by reaction of the methyl or ethyl ester of the acetic acid and ethylenediamine.

By interaction of 3-chloromethylthianaphthene, 2-aminopyridine and sodamide, 2-(3-thianaphthenylmethylamino)-pyridine was formed. When this substance was allowed to react with β-dimethylaminoethyl chloride and sodamide, N,N-dimethyl-N′-(2-pyridyl)-N′-(3-thianaphthenylmethyl)-ethylenediamine was produced.

The imidazolines are to be tested for pressor activity, and the substituted ethylenediamine for its possible antihistaminic effect. Although thianaphthene-3-acetic acid, unlike indole-3-acetic acid, was found to be of little value as a plant growth hormone,[7] it will be of interest to test thianaphthene-2-acetic acid and its esters for this type of action.

Experimental Part

3-Chloromethylthianaphthene.—A rapid stream of hydrogen chloride was passed into a vigorously stirred mixture of 97.0 g. (1.2 moles) of 37% aqueous formaldehyde, 97.0 cc. (1.1 moles) of concd. hydrochloric acid and 130.5 g. (0.97 mole) of thianaphthene until the mixture was saturated. During this time the temperature of the mixture rose to 65°. This temperature was maintained for one hour while a slow stream of hydrogen chloride was passed into the mixture. Water was added to the cold material, the organic layer separated, and the aqueous layer extracted with benzene. The combined organic layer and benzene extract was washed successively with water, sodium bicarbonate solution and water. Upon fractionation there was obtained 29.9 g. of thianaphthene and 101.2 g. of the chloromethyl derivative; b. p. 125–127° (2 mm.); yield 74.5% based on the thianaphthene which had reacted.

Anal. Calcd. for C_9H_7ClS: Cl, 19.41. Found: Cl, 19.68.

3-Cyanomethylthianaphthene.—A mixture of 18.3 g. (0.10 mole) of 3-chloromethylthianaphthene, 7.4 g. (0.15 mole) of sodium cyanide, 10 cc. of acetone and 10 cc. of water was refluxed for twelve hours. The reaction mixture was cooled, water added, the organic layer separated, and the aqueous layer extracted with ether. The combined organic layer and ether extract was washed with water, dried over anhydrous magnesium sulfate, and fractionated. There was obtained 9.2 g. (53%) of the cyanomethyl derivative, b. p. 138–140° (2 mm.); m. p. 66–67° after recrystallization from isopropyl alcohol–petroleum ether (40–60°).

Thianaphthene-3-acetic Acid.—A mixture of 28.0 g. (0.162 mole) of the cyanomethyl derivative, 19.4 g. (0.486 mole) of sodium hydroxide and 100 cc. of water was stirred vigorously and refluxed for fourteen hours.

---

[1] This paper represents part of a dissertation to be submitted to the Horace H. Rackham School of Graduate Studies by Mr. Sheets in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

[2] Monsanto Chemical Company Fellow.

[3] Hansch and Lindwall (*J. Org. Chem.*, **10**, 381 (1945)) stated that they were unable to chloromethylate thianaphthene.

[4] Crook and Davies, *J. Chem. Soc.*, 1697 (1937). Although these investigators named their acid, incorrectly, thianaphthene-2-acetic acid, its preparation from 3-bromothianaphthene, by a series of steps which include the Grignard and Arndt–Eistert reactions, establishes its structure as the 3-acetic acid.

[5] Weissgerber and Kruber, *Ber.*, **53**, 1551 (1920).

[6] It has been shown that Raney nickel will remove the sulfur atom from aliphatic sulfides (Mozingo, Wolf, Harris and Folkers, THIS JOURNAL, **65**, 1013 (1943); Snyder, Howe, Cannon and Nyman, *ibid.*, **65**, 2211 (1943); Snyder and Cannon, *ibid.*, **66**, 155 (1944)), from compounds which contain a thiophane nucleus such as biotin (du Vigneaud, Melville, Folkers, Wolf, Mozingo, Keresztesy and Harris, *J. Biol. Chem.*, **146**, 475 (1942)) and 2-(δ-carboxybutyl)-3,4-diaminothiophane (Harris, Mozingo, Wolf, Wilson and Folkers, THIS JOURNAL, **67**, 2102 (1945)). However, as far as we are aware, the elimination of sulfur from a thiophene by nickel has not been reported hitherto.

[7] Crook, Davies and Smith, *Nature*, **139**, 154 (1937).

The cold mixture was extracted with ether in order to remove unchanged nitrile and other products, and the alkaline layer was then heated with Norite, and filtered. After acidification, the precipitated acid was recrystallized from water. It was dissolved in sodium bicarbonate solution, the solution treated with Norite, filtered and the acid precipitated with hydrochloric acid; yield 16.1 g. (51.7%); m. p. 108–109°.[8]

Anal. Calcd. for $C_{10}H_8O_2S$: neut. equiv., 192.2. Found: neut. equiv., 193.0.

The amide, prepared from the acid chloride and recrystallized from water, melted at 171–173°.

2-(3-Thianaphthenylmethyl)-imidazoline Hydrochloride.—(a) A mixture of 5.2 g. (0.039 mole) of ethylenediamine dihydrochloride and 20.0 g. (0.330 mole) of anhydrous ethylenediamine[9] was placed in a flask to which an eight-inch column was attached. The column was connected to an inclined condenser. The mixture was stirred rapidly, and 15.0 g. (0.078 mole) of thianaphthene-3-acetic acid was added, and the temperature was raised gradually to 220° during a two-hour period. During the process, the excess ethylenediamine and water distilled from the flask and condensed. After the material had been heated at 220° for five minutes, water was added, and the mixture was then acidified with hydrochloric acid. After removal of insoluble material, the acidic solution was decolorized with 3.2 g. of Norite, made alkaline with 40% aqueous sodium hydroxide, the oily layer separated, and the aqueous layer extracted with ether. The combined oil and extract was washed with water, dried over magnesium sulfate, and then treated with hydrogen chloride. The precipitated hydrochloride (9.6 g., 49%) was recrystallized from absolute alcohol–acetone; m. p. 234–235°.

Anal. Calcd. for $C_{12}H_{13}ClN_2S$: Cl, 14.03; N, 11.08. Found: Cl, 13.99; N, 10.94.

(b) In order to obtain the required 3-thianaphthenylacetimino ethyl ether hydrochloride, a mixture of 1.00 g. (0.0058 mole) of 3-cyanomethylthianaphthene, 0.27 g. (0.0058 mole) of absolute alcohol and 2 cc. of anhydrous benzene was cooled in an ice-bath and treated with hydrogen chloride until the increase in weight of the mixture was 0.21 g. (This corresponds to 0.0058 mole of hydrogen chloride.) The material was kept in a refrigerator for twelve hours. Upon the addition of absolute ether, an oil precipitated. The liquid was decanted, the oil was triturated under ether whereupon it became solid; yield 1.0 g. (67%); m. p. 103° (dec.), but the molten material solidified again and melted at 167–168°.[10]

The temperature of a mixture of 1.0 g. of the imino ether hydrochloride and 1.0 g. of ethylenediamine (Eastman Kodak Co. 95–100%) was raised, gradually, to 200° during a period of two hours. After the excess diamine had distilled from the mixture, it was cooled whereupon it solidified. The product was dissolved in water and acidified with hydrochloric acid. The solution was treated with Norite, filtered, the filtrate made alkaline with 40% sodium hydroxide solution, and the organic material extracted with ether. After the solution had been dried over magnesium sulfate, it was treated with hydrogen chloride. The crude, yellow precipitated product melted at 198–204°; yield 0.24 g. (24.3%). The product melted at 234–235° after recrystallization from absolute alcohol–acetone.

N,N-Dimethyl-N'-(2-pyridyl)-N'-(3-thianaphthenylmethyl)-ethylene-diamine Hydrochloride.—A mixture of 9.4 g. (0.10 mole) of 2-aminopyridine, 100 cc. of dry toluene and 5.9 g. (0.15 mole) of powdered sodamide was stirred and refluxed for three hours. A solution of 18.3 g. (0.10 mole) of 3-chloromethylthianaphthene in 50 cc. of dry toluene was added, the mixture refluxed for ten hours, cooled, water added, the organic layer separated, and the aqueous layer extracted with ether. The combined organic layer and ether extract was washed with water, dried and distilled. There was obtained 15.0 g. (62.5%) of 2-(3-thianaphthenylmethylamino)-pyridine; b. p. 180–185° (1 mm.); m. p. 101–103° after recrystallization from ethanol–water.

Anal. Calcd. for $C_{14}H_{12}N_2S$: N, 11.66. Found: N, 11.88.

A mixture of 12.8 g. (0.053 mole) of the substituted pyridine, 3.1 g. (0.080 mole) of powdered sodamide and 150 cc. of dry toluene was refluxed for two hours. A toluene solution of β-dimethylaminoethyl chloride, prepared from 11.5 g. (0.080 mole) of the chloride hydrochloride, was added and the material refluxed for twelve hours. Water was added, the organic layer separated, and the aqueous layer extracted with ether. After combination of the organic layer and ether extract, and distillation, 12.7 g. (77%) of product was obtained; b. p. 169–170° (0.01 mm.). The oil was dissolved in ether, and treated with an ether solution which contained the calculated amount of hydrogen chloride. The precipitated monohydrochloride was recrystallized from acetone; m. p. 186–187°.

Anal. Calcd. for $C_{18}H_{22}ClN_3S$: Cl, 10.19; N, 12.08. Found: Cl, 10.31; N, 12.05.

Thianaphthene-2-acetic Acid, Methyl and Ethyl Ester.—Distilled thianaphthenyl-2-carbonyl chloride[5] (21.6 g., 0.11 mole), dissolved in 200 cc. of ether, was dropped into an ether solution which contained 13.8 g. (0.328 mole) of diazomethane during a period of one and one-half hours while the temperature of the mixture was maintained at 4–5°. After application of the Arndt–Eistert procedure,[11] the ethyl ester (17.9 g., 74%) which was obtained boiled at 150° (2 mm.).

Anal. Calcd. for $C_{12}H_{12}O_2S$: sapn. equiv., 220.3. Found: sapn. equiv., 217.6.

A portion of the ester was hydrolyzed with 10% sodium hydroxide solution. The acid, after recrystallization from carbon tetrachloride, melted at 141–142°.

Anal. Calcd. for $C_{10}H_8O_2S$: neut. equiv., 192.2. Found: neut. equiv., 191.0.

By the use of methanol in the Arndt–Eistert reaction, the methyl ester was obtained in 65% yield; b. p. 110–114° (0.01 mm.).

2-(2-Thianaphthenylmethyl)-imidazoline Hydrochloride.—(a) A mixture of 1.9 g. (0.01 mole) of thianaphthene 2-acetic acid, 0.8 g. (0.006 mole) of ethylenediamine dihydrochloride and 3.0 g. (0.05 mole) of anhydrous ethylenediamine was treated in the manner described above. The imidazoline hydrochloride (0.8 g., 32%) melted at 274–277° after recrystallization from butanol.

Anal. Calcd. for $C_{12}H_{13}ClN_2S$: Cl, 14.03; N, 11.08. Found: Cl, 14.01; N, 11.12.

(b) From 2.2 g. of ethyl thianaphthene-2-acetate, 0.8 g. of ethylenediamine dihydrochloride and 3.0 g. of ethylenediamine, 0.8 g. of the hydrochloride was obtained.

(c) A mixture of 2.0 g. (0.01 mole) of methyl thianaphthene-2-acetate, and 2.4 g. (0.04 mole) of anhydrous ethylenediamine was refluxed for eight hours, and then fractionated at 0.01 mm. pressure. The crude hydrochloride (1.0 g., 40%) melted at 270–275°.

Removal of Sulfur from Thianaphthene-2-carboxylic, Thianaphthene-2-acetic and Thianaphthene-3-acetic Acid.—A mixture of 1.8 g. (0.01 mole) of thianaphthene-2-carboxylic acid,[12] 2.5 g. of sodium carbonate, 500 cc. of distilled water and 38 g. of Raney nickel was heated at 75° for one-half hour. The cold mixture was filtered, the catalyst washed with dilute carbonate solution, and the filtrate neutralized to litmus with concd. hydrochloric acid. The solution was clarified with filter-cel, made slightly alkaline, and concentrated to a volume of about 25 cc. After acidification to congo red with hydrochloric acid, the precipi-

---

(8) Ref. 4, m. p. 109°.

(9) Prepared by dehydration of 95% aqueous ethylenediamine with sodium hydroxide.

(10) After recrystallization of the molten material from water it melted at 172–173°; mixed m. p. 171–173° with amide which had been prepared from thianaphthene-3-acetyl chloride.

(11) "Organic Reactions," Vol. I, p. 52.

(12) Schönberg, Petersen and Kaltschmitt, *Ber.*, **66**, 233 (1933).

tated oil was extracted with ether. The solvent was removed, and the residue dissolved in hot petroleum ether (60–75°) Crystalline β-phenylpropionic acid (1.4 g., 93.4%) separated from the cold solution; mixed m. p. with an authentic sample 48–49°.[13]

Anal. Calcd. for $C_9H_{10}O_2$: neut. equiv., 150.2. Found: neut. equiv., 150.7.

The amide, prepared from the acid chloride and ammonia, melted at 99–100°,[14] after recrystallization from water, and then from petroleum ether (60–75°); mixed m. p. 99–100°.

By the process described above, except that less catalyst was used (28.5 g. of Raney nickel for 0.01 mole of the acid), 1.9 g. of thianaphthene-2-acetic acid was converted into 1.4 g. (85%) of γ-phenylbutyric acid; m. p. 51–52°[15] without recrystallization.

Anal. Calcd. for $C_{10}H_{12}O_2$: neut. equiv., 164.2. Found: neut. equiv., 164.9.

The amide melted at 84–85°[16] after recrystallization from water.

By use of the above procedure, 1.9 g. of thianaphthene-3-acetic acid and 34 g. of Raney nickel yielded 1.6 g. (98%) of oily β-phenylbutyric acid.

Anal. Calcd. for $C_{10}H_{12}O_2$: neut. equiv., 164.2. Found: neut. equiv., 164.1.

The oily acid was converted to its acid chloride, and the latter treated with ammonia water; the amide melted at 104–105°[17] after recrystallization from water.

The anilide melted at 136–137°[18] after recrystallization from acetone–petroleum ether (60–75°).

Summary

The preparation of 3-chloromethylthianaphthene, thianaphthene-2- and thianaphthene-3-acetic acid has been described.

3-Chloromethylthianaphthene was converted into N,N-dimethyl-N′-(2-pyridyl)-N′-(3-thianaphthenylmethyl)-ethylenediamine hydrochloride.

From thianaphthene-2- and thianaphthene-3-acetic acid, the corresponding 2-(thianaphthenylmethyl)-imidazolines were obtained.

Sulfur can be removed from thianaphthenecarboxylic and thianaphtheneacetic acids with the formation, in high yields, of phenyl-substituted propionic and butyric acids, respectively.

---

[13] Merz and Weith (*Ber.*, **10**, 758 (1877)) reported 47°.

[14] Weerman and Jongkees (*Rec. trav. chim.*, **25**, 241 (1906)) found 99°.

[15] Semmler (*Ber.*, **39**, 728 (1906)) found 52°.

[16] Willgerodt and Merck (*J. prakt. Chem.*, [2] **80**, 197 (1909)) reported 84.5°.

[17] Kohler and Reimer (*Am. Chem. J.*, **33**, 353 (1905)) reported 105°.

[18] Eijkman (*Chem. Weekblad*, **5**, 657; *Chem. Centr.*, **79**, II, 1100 (1908)) found the same melting point.

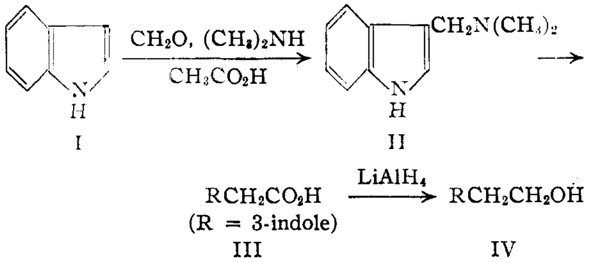
ANN ARBOR, MICHIGAN RECEIVED MAY 19, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Preparation of 3-Indoleacetic Acid; A New Synthesis of Tryptophol

BY H. R. SNYDER AND FREDERICK J. PILGRIM[1]

In a recently reported synthesis of *dl*-homotryptophan,[2] tryptophol [β-(3-indole)-ethanol, IV] was employed as an intermediate. In connection with that work it was of interest to develop a method of preparation of tryptophol more convenient than any previously described. A new synthesis has been accomplished as indicated in the accompanying diagram.



Tryptophol has been previously prepared by the method of Oddo and Cambieri,[2,3] which consists in the treatment of indole-magnesium bromide with ethylene oxide; by the method of Jackson,[4] which involves the Bouveault–Blanc reduction of 3-indoleacetic ester (prepared by treatment of indolemagnesium iodide with chloroacetonitrile,[5] hydrolysis of 3-indoleacetonitrile and subsequent esterification of 3-indoleacetic acid); and by the treatment of indolemagnesium iodide with ethylene chlorohydrin.[6]

Gramine (β-dimethylaminomethylindole, II) was prepared from indole (I) by the method of Kühn and Stein.[7] When gramine was treated with a boiling aqueous alcoholic solution of sodium cyanide for eighty hours, the reaction product was found to be a readily separable mixture of sodium 3-indoleacetate (80%) and 3-indoleacetamide (20%). The amide was smoothly converted to 3-indoleacetic acid (III) in high yield by hydrolysis with sodium hydroxide solution. The over-all yield of III from gramine (II) was nearly 90%. The treatment of dialkylaminomethyl derivatives of indole with sodium cyanide to produce 3-indoleacetic acid has been previously reported by Kühn and Andersag[8] but no experimental details of this work are available.

3-Indoleacetic acid was readily reduced to the

---

[1] **Present address:** Chas. Pfizer and Co., Inc., Brooklyn 6, N. Y.

[2] Snyder and Pilgrim, THIS JOURNAL, **70**, 1962 (1948).

[3] Oddo and Cambieri, *Gazz. chim. ital.*, **69**, 19 (1939).

[4] Jackson, *J. Biol. Chem.*, **88**, 659 (1930).

[5] Majima and Hoshino, *Ber.*, **58**, 2042 (1925).

[6] Hoshino and Shimodaira, *Ann.*, **520**, 19 (1935).

[7] Kühn and Stein, *Ber.*, **70**, 567 (1937).

[8] Described in Department of Commerce reports of German technological developments by Dr. W. Salzer (P. B. 706).