## [CONTRIBUTION FROM THE RICHARDSON CHEMICAL LABROATORY OF TULANE UNIVERSITY]

## Some 2-Substituted Thianaphthenes Derived from 2-Thianaphthenyllithium<sup>1</sup>

## By DAVID A. SHIRLEY AND MARGARET D. CAMERON<sup>2</sup>

2-Thianaphthenyllithium, readily prepared from the metalation of thianaphthene by n-butyllithium, has been examined in its reaction with a variety of types such as isocyanates, bromine, methyl p-toluenesulfonate and aldehydes. The amides formed from the reaction of 2-thianaphthenyllithium and certain isocyanates and from 2-thianaphthenecarboxylic acid were reduced to the corresponding amines with lithium aluminum hydride. The compounds produced have been tested for antitubercular chemotherapeutic activity.

While the synthesis of 3-derivatives of thianaphthene is readily accomplished by utilizing the normal aromatic substitution reactions, preparation of 2-substituted types is, in general, limited to ring closure reactions and metalation, the one substitution reaction which may occur predominately in the 2-position.<sup>3</sup> In an earlier paper from this laboratory,<sup>4</sup> we reported metalation of thianaphthene with *n*-butyllithium forming 2-thianaphthenyllithium.

In the present work, we have utilized the ready formation of the 2-lithio compound as a route to a series of 2-substituted types. In this work the yield of 2-thianaphthenyllithium was improved from the 55% reported earlier<sup>4</sup> to the range of 70-74% as determined by the amount of 2-thianaphthenecarboxylic acid formed with carbon dioxide. The derivatives prepared were selected in part on the basis of their possible biological activity, and all compounds have been tested by the Eli Lilly and Co. for antitubercular chemotherapeutic activity.

The reaction of 2-thianaphthenyllithium with bromine gave a 39% yield of 2-bromothianaph-thene and also a 16% yield of 2,2'-dithianaphthenyl. Alkylation of 2-thianaphthenyllithium with methyl *p*-toluenesulfonate gave 2-methylthianaphthene in 43% yield. The reaction of the organolithium with acetaldehyde, benzaldehyde, p-chlorobenzaldehyde, p-tolualdehyde and p-dimethylaminobenzaldehyde gave the corresponding carbinols as indicated in Table I. Thianaphthene-2-carboxamides were prepared by two different methods: the reaction of 2-thianaphthenyllithium with isocyanates and the reaction of amines with the carboxylic acid chloride prepared from thianaphthene-2-carboxylic acid. The isocyanates used in the former were phenyl and o-tolyl, while the amines used in the latter reaction were 2-aminopyridine, 2-aminothiazole, 2-aminopyrimidine, p-aminosalicylic acid and 4,4'-diaminodiphenyl sulfone. The data on these are summarized in Table II. Reduction of several of these amides with lithium aluminum hydride gave the corresponding secondary amines. No carbinols<sup>5</sup> were isolated from these reductions (Table III).

We are grateful to Dr. Reuben G. Jones of the Lilly Research Laboratories for arranging the (1) Abstracted in part from the Ph.D. dissertation of Margaret D. Cameron. pharmacological evaluation of the compounds reported here and to the Eli Lilly and Co. for financial support of this investigation. We would also like to express appreciation to Mr. Paul Kobetz for assistance.

## Experimental<sup>6</sup>

2-Thianaphthenyllithium.—The procedure which gives the improved yields of 70–74% 2-thianaphthenyllithium differs from that previously described<sup>4</sup> in that the mole ratio of tiffanaphthene to butyl bromide was increased to 2:3 and the reaction temperature for the formation of both the *n*butyllithium and the 2-thianaphthenyllithium was lowered by chilling the reaction vessel in an ice-hydrochloric acidbath.

2-Bromothianaphthene.—Sixteen grams (0.10 mole) of anhydrous bromine dissolved in 500 ml. of dry ether was added to an ethereal solution of 2-thianaphthenyllithium. The mixture was allowed to reflux for 30 minutes. The resulting ethereal solution was extracted twice with 500 ml. of 5% sodium hydroxide solution and then dried over calcium chloride. The ether was distilled off at atmospheric pressure and the residue fractionally distilled under reduced pressure. The fraction boiling 135-142° at 18 mm. was collected as 2-bromothianaphthene. Recrystallization from dilute ethanol gave 6.9 g. (39%) melting at 41-42°.

Anal. Calcd. for C<sub>8</sub>H<sub>5</sub>BrS: Br, 37.5. Found: Br, 37.3.

Repeated recrystallization from acetic acid of the solid remaining after distillation of the 2-bromothianaphthene gave 2.1 g. of 2,2'-dithianaphthenyl melting at 260-261°. Fries and Hemmecke' gave the melting point of 2,2'-dithianaphthenyl as 262°.

2-Methylthianaphthene.—A solution of 130 g. (0.70 mole)of methyl p-toluenesulfonate in 350 ml. of anhydrous ether was added with stirring and cooling to an ethereal solution of 2-thianaphthenyllithium (0.70 mole). Following the addition, the mixture was stirred for an hour and then heated under reflux for half an hour before being poured over 1500 ml. of crushed ice and water. The ether layer was separated and the aqueous layer extracted with three 250ml. portions of ether. The ethereal solutions were combined and dried over anhydrous magnesium sulfate. The ether was removed by distillation and the residue distilled under reduced pressure. A 60-ml. fraction boiling 135-150° (at *ca.* 80 mm.) was collected and recrystallized from ligroin and from ethanol to give 45 g. (43%) of 2-methylthianaphthene, m.p. 51.5-52°. The picrate, m.p. 108-109° was prepared. Hansch and Blondon,<sup>8</sup> who prepared 2-methylthianaphthene by ring closure reported its m.p. as 51-52° and that of its picrate as 108-109°. 2-Thianaphthenylcarbinols. Method A.—A solution of 45 g. (1.00 mole) of acetaldehyde (from freshly depolymer-

2-Thianaphthenylcarbinols. Method A.—A solution of 45 g. (1.00 mole) of acetaldehyde (from freshly depolymerized paraldehyde) in 100 ml. of cold anhydrous ether was slowly added, with stirring and chilling, to an ethereal solution of 2-thianaphthenyllithium (0.20 mole). The reaction mixture was refluxed for an hour and hydrolyzed by pouring into a liter of ice-water saturated with ammonium chloride. The ethereal layer was separated and the aqueous layer extracted with three 100-ml. portions of ether. The combined ethereal solutions were dried over anhydrous sodium carbonate, the ether removed by distillation, and the residue distilled under reduced pressure. The fraction boiling

<sup>(2)</sup> Eli Lilly and Co., Research Fellow, Tulane University, 1949-1951.

<sup>(3) (</sup>a) A. Schönberg, E. Peterson and H. Kaltschmitt, Ber., 66, 233 (1933); (b) R. Weissgerber and O. Kruber, *ibid.*, 53, 1551 (1920).

<sup>(4)</sup> D. A. Shirley and M. D. Cameron, THIS JOURNAL, 72, 2788 (1950).

<sup>(5)</sup> R. F. Nystrom and W. G. Brown, ibid., 70, 3738 (1948).

<sup>(6)</sup> Melting points were taken on a Fisher-Johns apparatus, unless otherwise noted. The yields are those of compounds in the melting point range given.

<sup>(7)</sup> K. Fries and E. Hemmecke, Ann., 470, 1 (1929)

<sup>(8)</sup> C. Hansch and W. A. Blondon, THIS JOURNAL, 70, 1561 (1948).

		TABLE	I					
2-THIANAPHTHENYL CARBINOLS CHOHR								
R	м.р., °С.	Method	Yield, %	Molecular Formula	S anal Calcd.	yses, % Found		
Methyl	58-58.3ª	Α	72	C10H10OS	18.0	18.1		
Phenyl	83	В	70	$C_{15}H_{12}OS$	13.3	13.5		
p-Tolyl	$56.5 - 57.5^{\circ}$	В	$Low^b$	C16H14OS	12.6	12.7		
<i>p</i> -Chlorophenyl	102 - 102.5	В	68	C <sub>15</sub> H <sub>11</sub> CIOS	11.7	11.7		
p-Dimethylaminophenyl <sup>c</sup>	137.5-138	В	47	C <sub>17</sub> H <sub>17</sub> NOS	11.3	11.2		

<sup>a</sup> Melting point taken by capillary tube method. <sup>b</sup> About 0.1 g. of pure crystalline material was obtained from 10.6 g. (42%) of semi-solid product which resulted from the crystallization attempts given in Method B. <sup>c</sup> Prepared by Mr. Paul Kobetz.

		Table II					
THIANAPHTHENE-2-CARBOXAMIDES							
R	M.p., °C.	Method	Vield, %	Molecular formula	N analy Calcd.	ses, % Found	
Phenyl	187.5 - 188.5	Α	81	C <sub>15</sub> H <sub>11</sub> NOS	5.53	5.55	
o-Tolyl	157.5 - 158	Α	41	C <sub>16</sub> H <sub>18</sub> NOS	5.24	5.32	
2-Pyridy1	132 - 132.5	В	<b>54</b>	$C_{14}H_{10}N_2OS$	11.02	11.06	
2-Thiazolyl	194.5 - 195	в	71	$C_{12}H_8N_2OS_2$	10.76	10.99	
2-Pyrimidyl	202 - 202.5	В	74	C13H9N3OS	16.46	16.39	
3-Hydroxy-4-carboxypheny	272.5 - 273	Bª	23	C <sub>16</sub> H <sub>11</sub> NO <sub>4</sub> S	4.47	4.56	
(4.4'-Diphenylene sulfone) <sup>1</sup> /»	333 dec.	B⁵	17	CanHoe NoO2S	5.22	5.12	

 $^{a}$  Recrystallized from acetic acid.  $^{b}4,4'$ -Di-(thianaphthene-2-carboxamido)-diphenyl sulfone was recrystallized from cyclohexanone, ordinary organic solvents having been found inadequate.

OTT NUTTO

TABLE III

2-AMINOMETHYLTHIANAPHTHENES

			S CH2NHR			
R	М.р., °С.	Method	Vield, %	Molecular formula	N analyses, Calcd. For	% ind
Hydrogen	58-59	А	58	C.H.NS	8.59 8.	52
Phenyl	113-113.5	в	42	C15H18NS	5.86 5.	94
o-Tolyl	69-69.5	в	26	$C_{16}H_{15}NS$	5.53 5.	51
2-Pyridyl	121.5-122	в	35	$C_{14}H_{12}N_2S$	11.66 11.	72
2-Thiazolyl	149.5-150	в	38	$C_{12}H_{10}N_2S_2$	11.38 11.	48

at 100-101° at 2 mm. was collected as the carbinol. Two recrystallizations from methanol gave 14.3 g. (72%) of methyl-2-thianaphthenylcarbinol, m.p. 58.0-58.3°. **Method B.**—A solution of 53.0 g. (0.50 mole) of benzalde-

Method B.—A solution of 53.0 g. (0.50 mole) of benzaldehyde in 100 ml. of anhydrous ether was added, with stirring and cooling, to an ethereal solution of 2-thianaphthenyllithium (0.19 mole). The reaction mixture was refluxed for half an hour, then hydrolyzed and separated as given in method A. The ethereal solutions were combined, dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. The oily residue was crystallized from warm ligroin and recrystallized twice from ethanol to give 31.5 g. (70%) of phenyl-2-thianaphthenylcarbinol melting at 83°.

Thianaphthene-2-carboxamides. Method A.—A solution of 2-thianaphthenyllithium (0.098 mole) was added with stirring and cooling to a solution of 25 ml. of phenyl isocyanate (0.177 mole) in 125 ml. of anhydrous ether. The mixture was refluxed for 15 minutes, cooled, and hydrolyzed by the addition of 100 ml. of cold, saturated ammonium chloride solution. The crude amide was removed by filtration and recrystallized from ethanol. Treatment with decolorizing charcoal and recrystallization from acctone gave 20.0 g. (81%) of N-phenylthianaphthene-2-carboxamide melting at 187.5–188.5°. By adding the isocyanate to the 2-thianaphthenyllithium, a considerably lower (22%) yield of amide was obtained. The 41% yield recorded in Table II for N-(o-tolyl)-thianaphthene-2-carboxamide was obtained by the latter modification.

Method B.—Thianaphthene-2-carboxylic acid (10.0 g. or 0.056 mole), prepared by carbonation of 2-thianaphthen-

yllithium,<sup>4</sup> was refluxed for one hour with 25 ml. of thionyl chloride. The excess thionyl chloride was removed by distillation under reduced pressure. To the solid residue were added 10 ml. of pyridine and 5.0 g. (0.050 mole) of 2-aminothiazole. The mixture was refluxed gently for two hours and then poured into 300 ml. of water. The crude amide was removed by filtration; acidification of the filtrate precipitated a small additional amount of amide, which was similarly removed. The amide was dissolved in ethanol, treated with charcoal, and recrystallized. A second recrystallization from ethanol gave 9.2 g. (71%) of N-(2'-thiazolyl)-thianaphthene-2-carboxamide melting at 194.5–195°.

2-Aminomethylthianaphthenes. Method A.—Thianaphthene-2-carboxamide (5.5 g. or 0.031 mole), prepared from the acid<sup>3</sup> was suspended in 80 ml. of anhydrous ether and slowly added with stirring to a chilled solution of 2.5 g. (0.066 mole) of lithium aluminum hydride in 150 ml. of anhydrous ether. On completion of the addition, the mixture was heated under reflux for 30 minutes. The mixture was cooled again and 4 ml. of water, 4 ml. of 25% sodium hydroxide solution and 15 ml. of water were added in that order with continued stirring and cooling. The ether was decanted from the granular inorganic residue and the residue was washed with three 100-ml. portions of ether. The ethereal solutions were combined and the ether removed by distillation. The solid residue was recrystallized from petroleum ether to give 2.9 g. (58%) of 2-aminomethylthianaphthene, m.p. 58-59°. Method B.—A solution of 3.25 g. (0.013 mole) of N-(2'pyridyl)-thianaphthene-2-carboxamide in 50 ml. of tetra-

Method B.--A solution of 3.25 g. (0.013 mole) of N-(2'pyridyl)-thianaphthene-2-carboxamide in 50 ml. of tetrahydrofuran was added with stirring and cooling to a solution of 3.0 g. of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The mixture was heated under reflux for three hours and hydrolyzed by the slow addition with cooling of 4 ml. of water in 20 ml. of tetrahydrofuran, 5 ml. of 25% sodium hydroxide solution and 50 ml. of water. The tetrahydrofuran solution was decanted from the residue, which was washed with three 100-ml. portions of tetrahydrofuran. The tetrahydrofuran was removed by distillation from the combined solution and washings. The residue was recrystallized twice from ethanol to give 1.1 g. (35%) of N-(2'-pyridyl)-aminomethylthianaphthene, m.p. 121.5-122°.

NEW ORLEANS 18, LOUISIANA RECEIVED AUGUST 6 1951