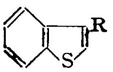
58. *Thiophen Derivatives of Potential Biological Interest. Part II. Thionaphthen Analogues of Stilbene and Related Compounds.*

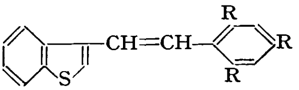
By Ng. Ph. Buu-Hoï and Ng. Hoán.

Numerous new derivatives of thionaphthen akin to stilbene and to αβ-diphenylacrylonitrile have been prepared by known methods for biological investigation; some contain another polycyclic radical in addition to the thionaphthen nucleus. During this work the properties of several thionaphthen aldehydes and ketones and of 3-thionaphthenylacetonitrile have been examined.

Substances of structure analogous to stilbene and bearing one or more polycyclic radicals are of interest in connection with a recent theory concerning the mode of action of carcinogens (Pinck, *Ann. New York Acad. Sci.*, 1948, **50**, 1). According to this theory, the action of tumour-producing substances, especially those with methyl or methylene groups, may involve biochemical conversion into ethylenic compounds and subsequent intervention of their external double bonds in chain reactions with certain cellular constituents.

A consequence of this theory is that more ethylenic compounds should be tested for carcinogenic properties; it is of interest in this respect that β-*sec.*-butyl-α-ethylstilbene has already been found to be carcinogenic (Dodds, *Brit. Med. Bull.*, 1947, **4**, 972). The present paper deals mainly with the preparation of substances akin to stilbene and containing the thionaphthen nucleus. The two thionaphthen intermediates used in this work were 3-formylthionaphthen (I; R = CHO), conveniently prepared by King and Nord's method (*J. Org. Chem.*, 1948, **13**, 635), and 3-thionaphthenylacetonitrile (I; R = CH_2·CN) (Avakian, Moss, and Martin, *J. Amer. Chem. Soc.*, 1948, **70**, 3075); 3-chloromethylthionaphthen (I; R = CH_2Cl), required for their preparation, was obtained by chloromethylation of thionaphthen according to the Darzens–Levy procedure (*Compt. rend.*, 1936, **202**, 73), which gave also a liquid unidentified dithionaphthenylmethane.

(I.) 

 (II.)

Reaction of 3-formylthionaphthen with benzylmagnesium chloride, followed by dehydration of the secondary alcohol thus formed, gave a liquid 3-styrylthionaphthen (II; R = H); reaction of the same aldehyde with 2 : 4 : 6-trinitrotoluene in the presence of piperidine, a procedure used in the aromatic series by Pfeiffer and Monath (*Ber.*, 1906, **39**, 1306), gave 3-(2 : 4 : 6-trinitrostyryl)thionaphthen (II; R = NO_2).

Another route to analogues of stilbene was the condensation of 3-formylthionaphthen in the presence of alkaline catalysts with arylacetonitriles. A series of α-aryl-β-3-thionaphthenylacrylonitriles (III) was thus easily prepared (see Table I); when 2-thienylacetonitrile was used in the latter process, α-2-thienyl-β-3-thionaphthenylacrylonitrile (IV) was obtained. Analogous condensation of various aromatic aldehydes with 3-thionaphthenylacetonitrile yielded a series of β-aryl-α-3-thionaphthenylacrylonitriles (V), listed in Table II along with a number of β-2-thienyl-α-3-thionaphthenylacrylonitriles of types (VI) and (VII) obtained similarly with various thiophen aldehydes. Mention should particularly be made of β-9-anthryl- (VIII) and β-3-pyrenyl-α-3-thionaphthenylacrylonitrile (IX), which represent highly condensed stilbene-like compounds, in the line of those postulated by Pinck (*loc. cit.*) as having a likelihood of carcinogenicity.

It is worth mention that, although β-*p*-methoxyphenyl-α-3-thionaphthenylacrylonitrile (as V) was readily demethylated by pyridine hydrochloride to the corresponding *p*-hydroxyphenyl compound, the *o*-methoxy-nitrile was converted by the same reagent into 3-3′-thionaphthenylcoumarin (X; R = H); 6-chloro- (X; R = Cl) and 6-bromo-3-3′-thionaphthenylcoumarin (X; R = Br) were also similarly prepared from β-(5-chloro-2-methoxyphenyl)- and β-(5-bromo-2-methoxyphenyl)-α-3′-thionaphthenylacrylonitrile. In the 5 : 6-benzocoumarin series, the compound (XI) could also be obtained from β-(2-methoxy-1-naphthyl)-α-3-thionaphthenylacrylonitrile in the same way. This confirms earlier observations on the formation of similar compounds in the aromatic and thiophen series (Buu-Hoï, Hoán, and Lavit, *J.*, 1950, 2130).

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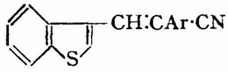

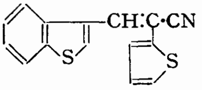

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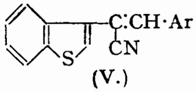

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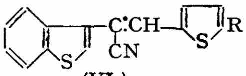

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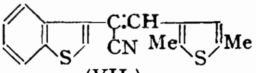
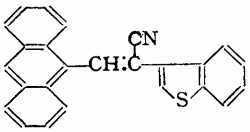
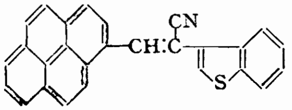


(VII.)

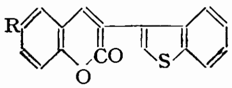
(VIII.)

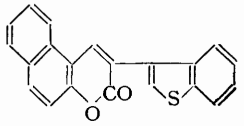




(IX.)

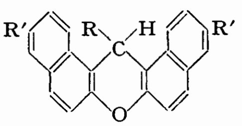
(X.)



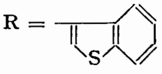


(XI.)

The ready accessibility of 3-formylthionaphthen by the Sommelet method led us to investigate its properties further. Nitration under conditions in which thiophen derivatives are attacked in the 2-position gave a single product, apparently 3-formyl-2-nitrothionaphthen. This reaction could be generalised to 3-acylthionaphthens, and 3-acetyl-2-nitro-, 2-nitro-3-propionyl-, and 3-*n*-butyryl-2-nitro-thionaphthen were thus readily obtained. 3-Thionaphthenylacetontrile gave no definite compound on nitration, but yielded easily an azomethine with 4-nitrosodimethylaniline.



(XII; R′ = H, XIII; R′ = Br,} R =



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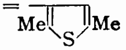
(XIV; R′ = H, R =



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As in the case of aromatic aldehydes (Claisen, *Annalen*, 1887, **237**, 270), 3-formylthionaphthen readily condensed with β-naphthol in the presence of mineral acid to give 5-3′-thionaphthenyl-3 : 4-6 : 7-dibenzoxanthen (XII); with 6-bromo-2-naphthol, the 2′ : 3″-dibromo-compound (XIII) was similarly obtained. This behaviour distinguishes 3-formylthionaphthen from

2-formylthiophen, which under the same conditions gave coal-like compounds, and relates it to 3-formyl-2 : 5-dimethylthiophen, which also readily gave 5-(2 : 5-dimethyl-3-thienyl)-3 : 4-6 : 7-dibenzoxanthen (XIV).

EXPERIMENTAL.

Preparation of Intermediates.—3-Chloromethylthionaphthen, prepared by the Darzens–Levy method (King and Nord, *loc. cit.*), was best isolated by dilution with water of the acetic acid medium containing the reaction product, and extraction by means of benzene, a solvent which does not take up acetic acid appreciably in the presence of water. The benzene solution was washed with dilute aqueous sodium hydrogen carbonate and dried (Na_2SO_4), the solvent removed in a vacuum, and the residue vacuum-distilled. After repeated recrystallisation from ligroin, it had m. p. 42° (lit., m. p. 39—40°). The higher-boiling by-products (b. p. 250—300°/13 mm.) crystallised partly. The solid removed had m. p. 216° after recrystallisation from ethanol, and its constitution is being investigated. The liquid part gave on redistillation a pale yellow viscous oil, b. p. 280—282°/13 mm., probably a *dithionaphthenylmethane* (Found : C, 72·4; H, 4·5. $C_{17}H_{12}S_2$ requires C, 72·9; H, 4·3%).

3-*Styrylthionaphthen.*—A solution of 3-formylthionaphthen (5 g.) in anhydrous ether (10 c.c.) was added in small portions to a cooled Grignard solution [from magnesium (1·8 g.) and benzyl chloride (10 g.) in ether (60 c.c.)]. A mixture of the crude carbinol thus obtained and 98% formic acid (20 c.c.) was refluxed for 5 minutes, then poured into water, and the styryl compound taken up in benzene and purified by vacuum-fractionation. It formed a pale yellow viscous oil, b. p. 238—242°/13 mm. (4·5 g.), which did not solidify even after prolonged storage and gave with sulphuric acid a dark green colour. This substance was apparently a mixture of the two possible stereoisomers of 3-styrylthionaphthen (Found : C, 81·0; H, 5·3. Calc. for $C_{16}H_{12}S$: C, 81·35; H, 5·1%).

3-(2 : 4 : 6-*Trinitrostyryl*)*thionaphthen.*—This *compound* was obtained in quantitative yield by refluxing a solution of 2 : 4 : 6-trinitrotoluene (1 g.) and 3-formylthionaphthen (1 g.) in dry benzene (10 c.c.) for 3 hours with 2 drops of piperidine; it formed, from ethanol, fine orange-red needles, m. p. 182°, giving with hot sulphuric acid a blue-violet colour (Found : N, 11·2. $C_{16}H_9O_6N_3S$ requires N, 11·3%).

Preparation of Acrylonitriles of Types (III), (IV), (V), (VI), *and* (VII).—Most of these were prepared by shaking a mixture of the aldehyde and the arylacetonitrile in warm ethanol with a few drops of 30% aqueous potassium hydroxide; the substances obtained were recrystallised from ethanol. In the case of *p*-nitrophenylacetonitrile, the alkaline catalyst was piperidine. *p*-Fluoro-, *p*-chloro-, and *p*-bromophenylacetontrile were best prepared by chloromethylation of fluoro-, chloro-, and bromo-benzene, and treatment of the corresponding chloromethyl compounds with sodium cyanide in ethanol–water. α- and β-Naphthylacetonitrile were best prepared from α- and β-methylnaphthalene by side-chain bromination with *N*-bromosuccinimide (Buu-Hoï, *Annalen*, 1944, **556**, 1), and subsequent treatment with sodium cyanide; 2-methoxy-1-naphthylacetonitrile (b. p. 230—235°/18 mm.) was similarly prepared from 1-chloromethyl-2-methoxynaphthalene (Badger, Carruthers, and Cook, *J.*, 1949, 1678). 2-Methoxy-1-naphthaldehyde, 3-formylacenaphthene, 9-anthraldehyde, 3-formylpyrene, and the thiophen aldehydes were prepared by the *N*-methylformanilide method. Demethylation of acrylontriles bearing methoxy-groups was effected in the usual way by refluxing the required methoxy-compound (1 part) with redistilled pyridine hydrochloride; after dilution with water, the precipitate formed was collected, washed with water, dried, and crystallised from benzene.

The *products* obtained are reported in Tables I and II.

3-3′-*Thionaphthenylcoumarin* (X; R = H).—A mixture of β-*o*-methoxyphenyl-α-3-thionaphthenylacrylontrile (1 g.) and pyridine hydrochloride (5 g.) was refluxed for 15 minutes. After dilution with water, the precipitate (1 g.) was collected, washed thoroughly with water, dried, and recrystallised from benzene; fine yellowish needles, m. p. 181°, insoluble in aqueous sodium hydroxide, were thus obtained (Found : C, 73·1; H, 3·5. $C_{17}H_{10}O_2S$ requires C, 73·4; H, 3·6%).

6-*Bromo*-3-3′-*thionaphthenylcoumarin* (X; R = Br) was similarly obtained from β-(5-bromo-2-methoxyphenyl)-α-3-thionaphthenylacrylonitrile, and formed from benzene a yellowish microcrystalline powder, m. p. 223° (Found : C, 56·7; H, 2·8. $C_{17}H_9O_2SBr$ requires C, 57·1; H, 2·5%). The 6-chloro-compound was obtained similarly in an impure state and had m. p. 175—180°.

3-3′-*Thionaphthenyl*-5 : 6-*benzocoumarin* (XI) crystallised from ethanol–benzene as fine shiny yellow needles, m. p. 222° (Found : C, 76·5; H, 3·6. $C_{21}H_{12}O_2S$ requires C, 76·8; H, 3·7%).

α-p-*Dimethylaminoanilo*-α-3-*thionaphthenylacetonitrile.*—A solution of *p*-nitrosodimethylaniline (0·5 g.) and 3-thionaphthenylacetonitrile (0·9 g.) in ethanol was treated with 2 drops of a concentrated solution of potassium hydroxide in ethanol. The precipitate of *anilo*-derivative obtained formed, from ethanol, fine violet-red prisms, m. p. 164° (Found : N, 13·4. $C_{18}H_{15}N_3S$ requires N, 13·7%).

5-3′-*Thionaphthenyl*-3 : 4-6 : 7-*dibenzoxanthen* (XII).—A solution of β-naphthol (2 g.) and 3-formylthionaphthen (1 g.) in boiling acetic acid (20 c.c.) was treated with a few drops of concentrated hydrochloric acid. The dark oil formed solidified after cooling; after repeated crystallisation from acetic acid, colourless needles, m. p. 280°, of the *dibenzoxanthen* were obtained (Found : C, 83·6; H, 4·2. $C_{29}H_{18}OS$ requires C, 84·0; H, 4·3%).

2′ : 3′′-*Dibromo*-5-3′-*thionaphthenyl*-3 : 4-6 : 7-*dibenzoxanthen.*—Similarly obtained from 6-bromo-2-naphthol (3·2 g.) and 3-formylthionaphthen (1 g.), this *compound* formed, from acetic acid, fine colourless needles, m. p. 325° (Found : C, 60·5; H, 2·9. $C_{29}H_{16}OSBr_2$ requires C, 60·8; H, 2·8%).

5-(2 : 5-*Dimethyl*-3-*thienyl*)-3 : 4-6 : 7-*dibenzoxanthen* (XIV).—This *dibenzoxanthen*, prepared from 2 : 5-dimethyl-3-formylthiophen (1 g.) and β-naphthol (2 g.), formed colourless prisms, m. p. 225°, from acetic acid (Found : C, 82·4; H, 5·2. $C_{27}H_{20}OS$ requires C, 82·6; H, 5·1%).

3-*Formyl*-2-*nitrothionaphthen*.—To a well-stirred, ice-cooled solution of 3-formylthionaphthen (9 g.) in acetic anhydride (50 c.c.), a mixture of fuming nitric acid (*d* 1·49) and acetic acid (40 c.c.) was added dropwise. After 15 minutes, the reaction product was poured on cracked ice; the precipitate formed after some hours was collected, thoroughly washed with water, and recrystallised from ethanol, giving pale yellow needles (7 g.), m. p. 124° (Found : C, 51·9; H, 2·5. $C_9H_5O_3NS$ requires C, 52·1; H, 2·4%).

TABLE I.

Acrylonitriles (III) *and* (IV).

			Found, %.		Reqd., %.	
β-3-Thionaphthenylacrylonitrile.[a]	M. p.	Formula.	C.	H.	C.	H.
α-Phenyl-	132°	$C_{17}H_{11}NS$	78·0	4·3	78·2	4·2
α-*p*-Tolyl-	139	$C_{18}H_{13}NS$	78·5	4·8	78·5	4·7
α-*p*-Ethylphenyl-	115	$C_{19}H_{15}NS$	78·6	5·4	78·9	5·2
α-*p*-Chlorophenyl-	180	$C_{17}H_{10}NSCl$	68·9	3·7	69·0	3·4
α-*p*-Bromophenyl-	175	$C_{17}H_{10}NSBr$	59·8	2·9	60·0	2·9
α-*p*-Methoxyphenyl-	118	$C_{18}H_{13}NOS$	74·0	4·8	74·2	4·5
α-*p*-Hydroxyphenyl-	202	$C_{17}H_{11}NOS$	73·2	4·0	73·6	4·0
α-*p*-Nitrophenyl-[b]	209	$C_{17}H_{10}N_2O_2S$	66·5	3·0	66·7	3·3
α-1-Naphthyl-	144	$C_{21}H_{13}NS$	80·9	4·4	81·0	4·2
α-2-Naphthyl-	179	$C_{21}H_{13}NS$	81·0	4·2	81·0	4·2
α-(2-Methoxy-1-naphthyl)-	147	$C_{22}H_{15}ONS$	77·6	4·6	77·4	4·4
α-2-Thienyl-	105	$C_{15}H_9NS_2$	67·3	3·5	67·4	3·4
α-3-Thionaphthenyl-	203	$C_{19}H_{11}NS_2$	71·8	3·8	71·9	3·5

[a] All shiny yellow needles, unless otherwise stated; all gave with sulphuric acid halochromic colours ranging from yellow to brown. [b] Orange.

TABLE II.

Acrylonitriles (V), (VI), *and* (VII).

			Found, %.		Reqd., %.	
α-3-Thionaphthenylacrylonitrile.[a]	M. p.	Formula.	C.	H.	C.	H.
β-Phenyl-	114°	$C_{17}H_{11}NS$	78·2	4·4	78·2	4·2
β-*p*-Chlorophenyl-	146	$C_{17}H_{10}NClS$	68·9	3·6	69·0	3·3
β-*m*-Nitrophenyl-	150	$C_{17}H_{10}O_2N_2S$	66·6	3·5	66·7	3·3
β-*p*-Fluorophenyl-	154	$C_{17}H_{10}NFS$	72·8	3·8	73·1	3·6
β-*o*-Methoxyphenyl-	125	$C_{18}H_{13}ONS$	74·4	4·4	74·6	4·5
β-*p*-Methoxyphenyl-	97	$C_{18}H_{13}ONS$	74·4	4·6	74·6	4·5
β-*p*-Hydroxyphenyl-	184	$C_{17}H_{11}ONS$	73·3	4·0	73·6	4·0
β-3 : 4-Dichlorophenyl-	153	$C_{17}H_9NCl_2S$	61·8	2·9	61·8	2·7
β-2 : 4-Dichlorophenyl-	142	$C_{17}H_9NCl_2S$	61·6	2·8	61·8	2·7
β-3 : 4-Dimethoxyphenyl-	143	$C_{19}H_{15}O_2NS$	70·8	4·7	71·0	4·6
β-3 : 4-Dihydroxyphenyl-	155	$C_{17}H_{11}O_2NS$	69·6	3·8	69·6	3·7
β-(5-Chloro-2-methoxyphenyl)-	146	$C_{18}H_{12}ONClS$	65·6	3·8	65·9	3·6
β-(5-Bromo-2-methoxyphenyl)-	164	$C_{18}H_{12}ONBrS$	58·6	3·5	58·4	3·2
β-1-Naphthyl-	138	$C_{21}H_{13}NS$	80·9	4·4	81·0	4·2
β-2-Naphthyl-	148	$C_{21}H_{13}NS$	80·8	4·4	81·0	4·2
β-3-Acenaphthenyl-[b]	176	$C_{23}H_{15}NS$	81·9	4·5	81·9	4·4
β-9-Anthryl-[b]	220	$C_{25}H_{15}NS$	83·2	4·0	83·1	4·1
β-3-Pyrenyl-[b]	231	$C_{27}H_{15}ONS$	84·0	3·8	84·2	3·9
β-2-Furyl-	94	$C_{15}H_9ONS$	71·4	3·4	71·7	3·6
β-2-Thienyl-	124	$C_{15}H_9NS_2$	67·3	3·5	67·4	3·4
β-(5-Methyl-2-thienyl)-	134	$C_{16}H_{11}NS_2$	68·0	3·6	68·0	3·9
β-(2 : 5-Dimethyl-3-thienyl)-	123	$C_{17}H_{13}NS_2$	69·8	4·4	69·9	4·2
β-(5-Chloro-2-thienyl)-	185	$C_{15}H_8NClS_2$	59·6	2·8	59·6	2·6
β-(5-Bromo-2-thienyl)-	183	$C_{15}H_8NBrS_2$	51·6	2·5	52·0	2·3
β-3 : 4-Dioxymethylenephenyl-	112	$C_{18}H_{11}O_2NS$	70·5	3·6	70·8	3·6
β-(2-Methoxy-1-naphthyl)-	151	$C_{22}H_{15}ONS$	77·0	4·6	77·4	4·4

[a] Yellow needles unless otherwise stated. All gave with sulphuric acid a colour ranging from yellow to violet; the hydroxy-compounds dissolved in aqueous sodium hydroxide to give yellow solutions. [b] Orange.

Nitration of 3-*Acylthionaphthens*.—This was effected as for the aldehyde; 3-acetyl-, 3-propionyl-, and 3-*n*-butyryl-thionaphthen were prepared according to Buu-Hoï and Cagniant (*Rec. Trav. chim.*, 1948, **67**, 64). Crystallisation of the products from ethanol gave 3-*acetyl*-2-*nitrothionaphthen*, fine yellow prisms, m. p. 179° (Found : C, 54·0; H, 3·0. $C_{10}H_7O_3NS$ requires C, 54·3; H, 3·1%) (with bromine in chloroform this gave a substitution product, m. p. 192°), 2-*nitro*-3-*propionylthionaphthen*, pale yellow prisms, m. p. 145° (Found : C, 56·0; H, 4·0. $C_{11}H_9O_3NS$ requires C, 56·1; H, 3·8%), and 3-n-*butyryl-2-nitrothionaphthen*, long pale yellow needles, m. p. 107° (Found : C, 57·6; H, 4·7. $C_{12}H_{11}O_3NS$ requires C, 57·8; H, 4·4%).

3-p-*Anisoylthionaphthen*.—In connection with the study of thionaphthenyl ketones, 3-*p*-anisoylthionaphthen was prepared from thionaphthen (15 g.), anisoyl chloride (21 g.), and aluminium chloride (17 g.) in carbon disulphide (150 c.c.). The ketone (20 g.) formed, from ethanol, yellowish prisms, m. p. 112°, b. p. 275—285°/13 mm., giving a yellow colour in sulphuric acid (Found : C, 71·4; H, 4·6. $C_{16}H_{12}O_2S$ requires C, 71·6; H, 4·5%). Demethylation by means of pyridine hydrochloride in the usual way gave 3-p-*hydroxybenzoylthionaphthen*, crystallising from benzene in almost colourless needles, m. p. 185—187°, giving yellow solutions in alkali (Found : C, 70·5; H, 4·0. $C_{15}H_{10}O_2S$ requires C, 70·8; H, 3·9%).

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