A NEW SYNTHESIS OF THIOPHENES AND THIAPYRANS

Part IV. Thiophenes and Thiapyrans from Naphthalene Thiols

By B. D. Tilak

(*Department of Chemical Technology, University of Bombay*)

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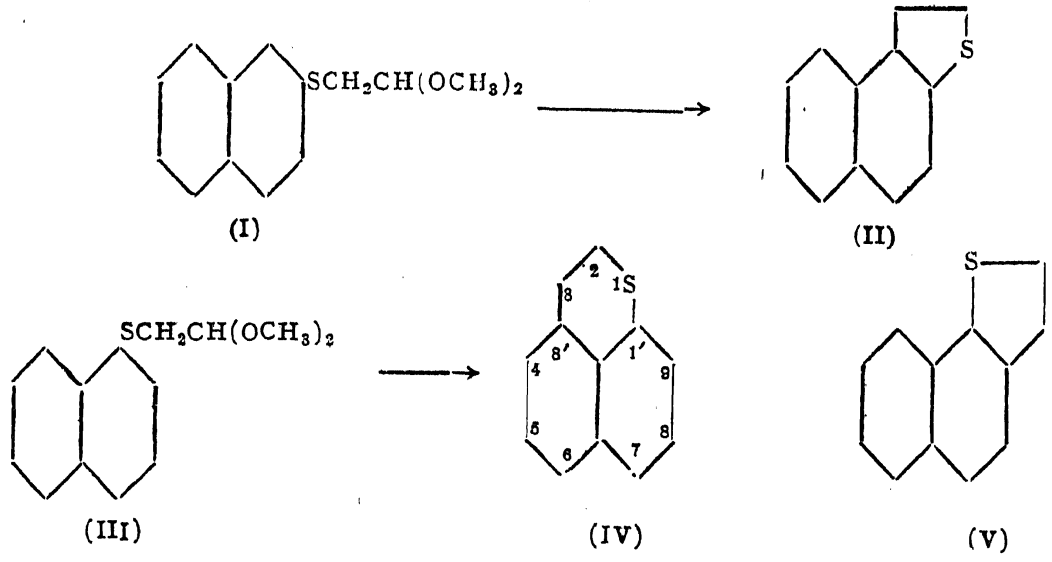
The syntheses of thionaphthene and its derivatives from thiophenol and substituted thiophenols have been described in the previous communications.[1] Syntheses of more complex thiophenes and thiapyrans starting from naphthalene mono and dithiols are now described.

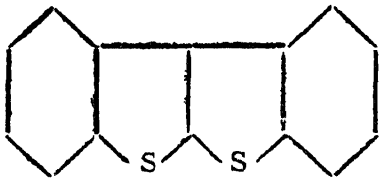
β-Naphthyl ω-dimethoxyethyl sulphide (I), obtained by the condensation of β-thionaphthol with bromoacetaldehyde dimethyl acetal, gave 4:5-benzothionaphthene (II) by cyclization in the reactive α-position. The latter compound has been prepared earlier by the reduction of the corresponding 3-hydroxy derivative, which is obtained by the α-ring closure of β-thionaphthoxyacetic acid.[2] An alternative route to (II) consists in the decarboxylation of 4:5-benzothionaphthene-2:3-dicarboxylic acid.[2]



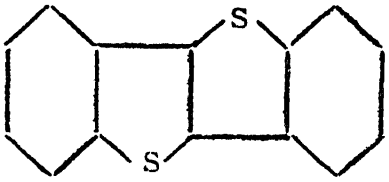
Ring-closure of α-naphthyl ω-dimethoxyethyl sulphide (III) gave a product, which being different from 6:7-benzothionaphthene[3] (V), is consti-

tuted as naphtho-(1′: 8′-*bc*)-thiapyran (IV). An unambiguous synthesis of (V) will be reported separately.[4]

Tetracyclic compounds containing two thiophene or thiapyran rings and two benzene or one naphthalene ring are unknown, with the probable exception of the pyrolysis product of *S*-acetylthiosalicylic acid for which the structures (VI) or (VII) have been suggested.[5] These compounds are of interest as potential carcinogens, *e.g.*, (VI) is the sulphur isoster of the carcinogenic hydrocarbon, 3 : 4-benzophenanthrene. Application of the new synthesis to naphthalene-1 : 5 and 2 : 6-dithiols has led to such tetracyclic compounds.

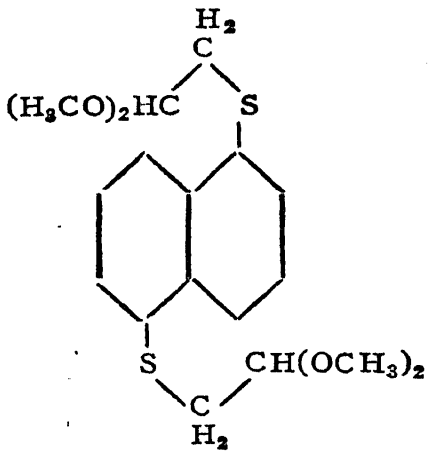


(VI)

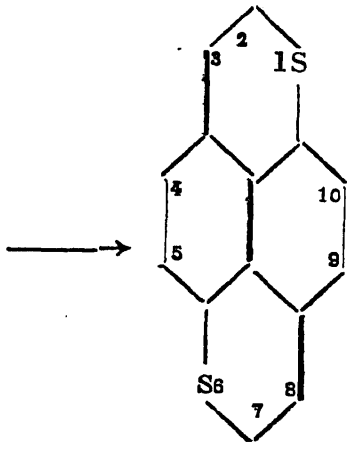


(VII)

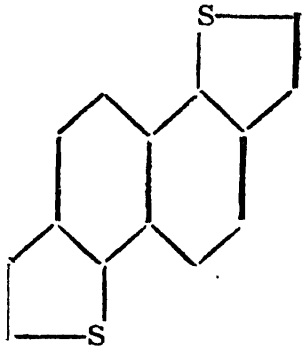
Naphthalene-1 : 5-dithiol was prepared in 85% yield by an improvement of the method of Albenga and Corbellini.[6] Reaction of the dithiol with two molecules of bromoacetaldehyde dimethyl acetal, gave 1 : 5-*bis*-dimethoxyethylmercapto-naphthalene (VIII). On ring-closure, the latter gave an orange-coloured product which is constituted as (IX) and named "1 : 6-dithiapyrene" from its apparent structural similarity to pyrene. Cyclization of (VIII) takes place in the *peri* positions, because β-cyclization would have led to 6 : 7, 7′ : 6′-dithionaphthene (X), an isoster of chrysene (XIII), which would probably be a colourless substance.



(VIII)

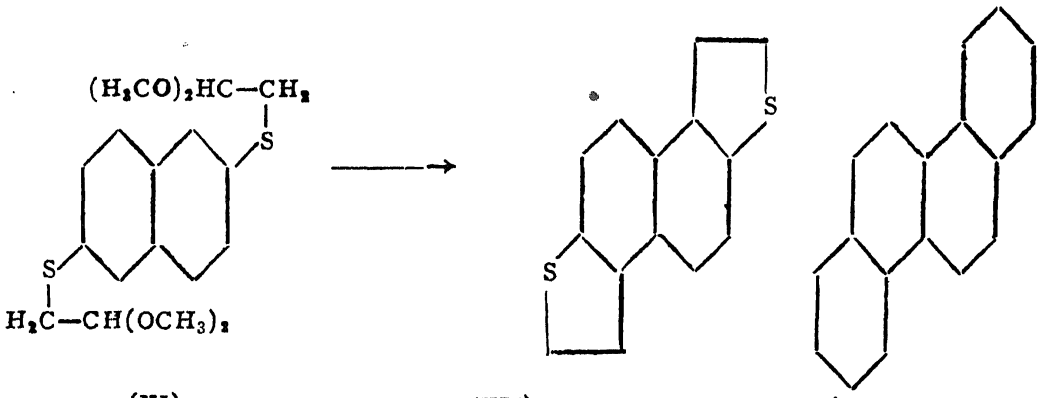


(IX)



(X)

The *peri*-ring-closure of (VIII) to give the orange-coloured compound (IX) is supported by the fact that the sulphur isoster (XII) of chrysene is colourless. 2 : 6-*Bis*-dimethoxyethylmercapto-naphthalene (XI) cyclized in the reactive α-positions to give 4 : 5, 5′ : 4′-dithionaphthene (XII).



(XI) (XII) (XIII)

Confirmation of the similarity of (XII) to chrysene was afforded by the resemblance in the absorption spectra of the two compounds (Fig. 1). The dissimilarity between the absorption spectrum of (IX) and the absorption spectra of (XI) and chrysene is an added proof of the *peri*-cyclization of (VIII) (Fig. 2).

Dr. Berenblum has examined (IX) and (XII) for their carcinogenic properties. Both the compounds were found to be inactive.

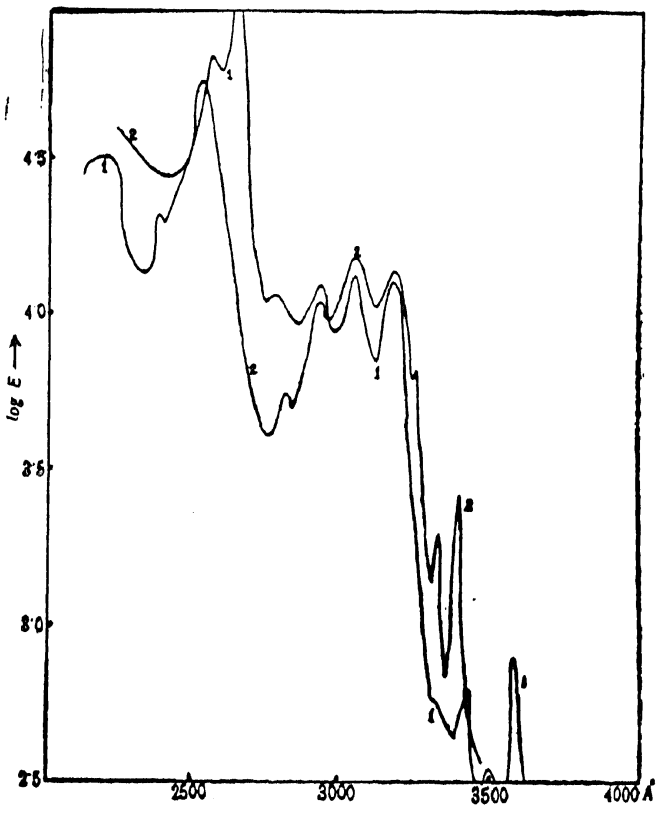


FIG. 1

(1) Chrysene (2) 4: 5, 5′: 4′—Dithionaphthene (XI).
Solvent—Methyl alcohol

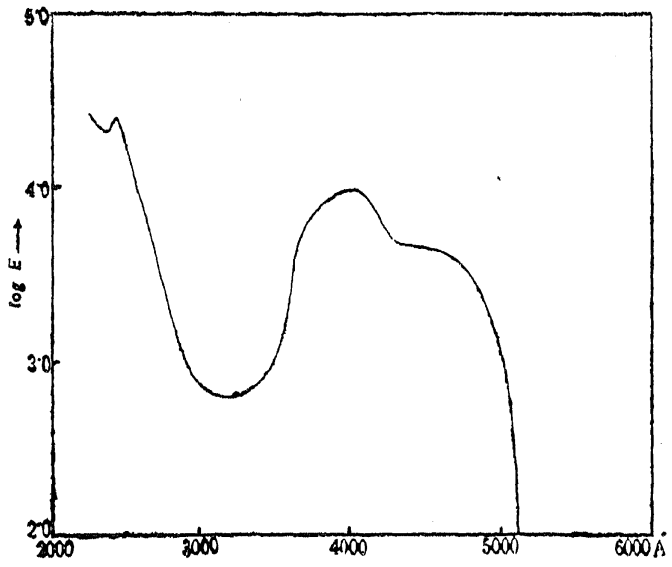


FIG. 2

1: 6—Diathiapyrene (IX) Solvent—Methyl alcohol

EXPERIMENTAL

(Analyses are by Drs. Weiler and Strauss, Oxford. M.ps. are uncorrected.)

The cyclization of the liquid sulphides (I) and (III) was effected according to the general procedure outlined earlier.[1] They were characterized as the 2:4-dinitrophenylhydrazones of the parent *S*-naphthylthioglycolic-aldehydes. The sulphides (VIII) and (XI) also gave the corresponding *bis*-2:4-dinitrophenylhydrazones which, however, could not be purified.

β-Naphthyl ω-dimethoxyethyl sulphide (I).—β-Thionaphthol[7] (4·8 g.), sodium (0·7 g.), sodium iodide (0·45 g.), bromoacetaldehyde dimethyl acetal (5·1 g.), and absolute alcohol (70 c.c.) were boiled for 6 hours. The etherial solution of the reaction product after concentration, gave a brown solid which after crystallization gave lustrous colourless flakes, m.p. 138–39°, of di-β-naphthyl disulphide. The mother-liquor gave the sulphide as a colourless liquid, b.p. 158–60° (bath temp.)/0·1 mm. (2·82 g.). In spite of repeated distillations it could not be obtained in the analytically pure state. *2:4-Dinitrophenylhydrazone* gave small yellow-orange rods from benzene, m.p. 174° (Found: N, 14·4. $C_{18}H_{14}N_4O_4S$ requires N, 14·7%).

4:5-*Benzothionaphthene* (*II*).—The sulphide (I) (2·17 g.) was added to phosphorus pentoxide (15 g.) and phosphoric acid (9 c.c.) at 150°/0·1 mm. and the white solid obtained was dissolved in ether. After washing with water, the ether was removed when 4:5-benzothionaphthene was obtained, m.p. 114-15° (0·66 g.). Lustrous colourless flakes from light petroleum (60–80°), m.p. 116-17°. Mayer[2] gives m.p. 108–09° (Found: C, 78·6; H, 4·5. Calc. for $C_{12}H_8S$: C, 78·3; H, 4·4%). The phosphoric acid residue

after dilution with water, gave a further quantity of 4:5-benzothionaphthene which was isolated by ether and crystallized, m.p. 106–12° (0·22 g.). The *picrate* crystallized from alcohol in orange needles, m.p. 151° (Found: S, 8·1. $C_{18}H_{11}N_3O_7S$ requires S, 7·8%).

α-Naphthyl ω-dimethoxyethyl sulphide (*III*).—α-Thionaphthol[7] (9·8 g.), sodium (1·4 g.), sodium iodide (0·92 g.), bromoacetal (10·4 g.) and absolute alcohol (60 c.c.) were boiled for 2 hours. The reaction product (13·5 g.) after fractionation gave: (*a*) colourless liquid, b.p. 130–50° (bath temp.)/3 mm.; (*b*) pale yellow liquid, b.p. 170–80° (bath temp.)/3 mm. (10·3 g.). Fraction (*a*) was identical with di-α-naphthyl disulphide and fraction (*b*) after two redistillations gave the sulphide as a pale straw-coloured liquid, b.p. 175–80° (bath temp.)/2·5 mm. (Found: C, 68·0; H, 6·7. $C_{14}H_{16}O_2S$ requires C, 67·8; H, 6·5%). 2:4-*Dinitrophenylhydrazone* gave yellow microcrystalline powder from benzene, m.p. 184·5–85·5° (Found: N, 14·7. $C_{18}H_{14}N_4O_4S$ requires N, 14·7%).

Naphtho-(1′:8′-*bc*)-*thiapyran* (*IV*).—The sulphide (III) (2·46 g.) was added to a mixture of phosphorus pentoxide (15 g.) and phosphoric acid (9 c.c.) at 170–80°/2 mm. and the lemon-yellow liquid (0·97 g.) which distilled over was treated with alcoholic solution of picric acid (3·3 g.). The picrate was treated with 5% caustic soda solution and the mixture steam-distilled. Naphtho-(1′:8′-*bc*)-thiapyran was isolated by means of ether and distilled when it gave a greenish-yellow liquid, b.p. 150–55° (bath temp.)/1·5–2 mm. (Found: C, 78·2; H, 4·6. $C_{12}H_8S$ requires C, 78·3; H, 4·4%). The *picrate* crystallized in olive-brown needles from alcohol, m.p. 177–78° (Found: N, 10·6. $C_{18}H_{11}N_3O_8S$ requires N, 10·2%).

Naphthalene-1:5-*dithiol*.—An intimate mixture of naphthalene-1:5-disulphonic acid (40 g.) and phosphorus pentachloride (160 g.) was heated in an oil bath at 140–50° for 3 hours. Phosphorous oxychloride was removed by distillation under reduced pressure and the residue was added to crushed ice. The crude sulphonyl chloride gave colourless needles, m.p. 182–83° (22·0 g.) from benzene. The benzene mother-liquor on concentration, gave an impure crop of the sulphonyl chloride (5·6 g.).

The disulphonyl chloride was reduced to the dithiol in 85% yield by a modification of the method of Albenga and Corbellini[6] who obtained it in 50% yield. Absolute alcohol (230 c.c.) was saturated with dry hydrogen chloride at room temperature in a three-necked flask fitted with a reflux condenser and a calcium chloride tube. Hydrated stannous chloride (115 g.) was added and the solution brought to boil. The disulphonyl chloride (23 g.) in boiling benzene (250 c.c.) was gradually added. A vigorous reaction set in after each addition of the sulphonyl chloride. Dry hydrogen chloride was

passed through the reaction mixture throughout the experiment. The mixture was finally refluxed for 30 minutes and then distilled till 210 c.c. of the solvent distilled over. The residue gave lustrous pale yellow flakes of naphthalene-1 : 5-dithiol on cooling. The dithiol was collected on a sinter glass crucible, washed repeatedly with concentrated hydrochloric acid (total 115 c.c.), then with water and finally dried in vacuum over phosphorus pentoxide. The dithiol (11·5 g.) gave m.p. 118–20°. Albenga and Corbellini quote m.p. 119°.

1 : 5-Bis-*dimethoxyethylmercapto-naphthalene* (*VIII*).—Naphthalene-1 : 5-dithiol (5·76 g.), sodium (1·65 g.), sodium iodide (1 g.), bromoacetal (10·14 g.) and absolute alcohol (50 c.c.) were refluxed for 3 hours. After removal of alcohol, the residue was extracted with ether and the extract was concentrated when colourless flat needles of 1 : 5-*bis*-dimethoxyethylmercapto-naphthalene separated, m.p. 66–69° (4·46 g.), raised to 69–70° on further recrystallization from the same solvent (Found: C, 59·3; H, 6·5; S, 17·5. $C_{18}H_{24}O_4S_2$ requires C, 58·7; H, 6·5; S, 17·4%).

1 : 6-*Dithiapyrene* (*IX*).—Phosphoric acid (14·5 c.c.) was added to a mixture of phosphorus pentoxide (24 g.) and (VIII) (3 g.) and the mixture was immediately heated for 10 minutes in an oil-bath kept at 140–50°. The mixture was poured over crushed ice and the precipitate (2·1 g.) obtained was extracted repeatedly with boiling benzene. The benzene solution after decolourization and concentration (about 15 c.c.), gave lustrous orange needles of 1 : 6-dithiapyrene, m.p. 224–25° (65 mg.), unaltered by further recrystallizations. The mother-liquor gave 75 mg. of the crude material after removal of the solvent. A solution of the above product, m.p. 224–25°, in benzene gave a uniform chromatogram when passed through activated alumina indicating its homogeneity, and the product, thus purified, gave the same melting point as the product before chromatographic separation (Found: C, 70·1; H, 3·3; S, 26·6. M.W., 238. $C_{14}H_8S_2$ requires C, 70·0; H, 3·3; S, 26·7%; M.W., 240). *sym-Trinitrobenzene derivative* crystallized in lustrous black needles from benzene, m.p. 213–14° (Found: C, 53·5; H, 2·6. $C_{20}H_{21}N_3O_6S_2$ requires C, 53·0; H, 2·4%).

2 : 6-Bis-*dimethoxyethylmercapto-naphthalene* (*XI*).— Naphthalene-2 : 6-dithiol (4·05 g.), prepared as the 1 : 5-isomer, was boiled with sodium (1 g.), sodium iodide (0·3 g.), bromoacetal (7·13 g.), and absolute alcohol (50 c.c.) for 3 hours. The mixture was worked up as in (VIII). 2 : 6-*Bis*-dimethoxyethylmercapto-naphthalene gave colourless crystals from ether, m.p. 89–92° (3·23 g.), and a second crop of the product was also collected, m.p. 87–90° (1·0 g.). After recrystallization, colourless flakes were obtained, m.p. 92–93° (Found: C, 59·0; H, 6·5; S, 17·0. $C_{18}H_{24}O_4S_2$ requires C, 58·7; H, 6·5; S, 17·4%).

4:5, 5′:4′-*Dithionaphthene* (*XII*).—Phosphoric acid (14·5 c.c.) was added to phosphorus pentoxide (24 g.) and (XI) (3·0 g.), and the mixture immediately heated at 140–50° for 5 minutes and then worked up as in (IX). The reaction product (1·49 g.) was repeatedly extracted with hot benzene, and the benzene solution, after decolourization and concentration, gave pale yellow flat needles, m.p. 252–62° (0·42 g.). A solution of the latter in benzene was passed through a column of activated alumina, and the first fraction showing pale blue-violet fluorescence in ultra-violet light was collected. After concentration to about 15 c.c., the solution gave 4:5, 5′:4′-dithionaphthene as lustrous colourless flakes, m.p. 263–65° (0·31 g.), raised to 264–65° by further recrystallization (benzene) (Found: C, 70·2; H, 3·4; S, 26·2. $C_{14}H_8S_2$ requires C, 70·0; H, 3·3; S, 26·7%). The *sym-trinitrobenzene* derivative gave slender orange needles from benzene, m.p. 200–201° (Found: C, 53·0; H, 2·2. $C_{20}H_{11}N_3O_6S_2$ requires C, 53·0; H, 2·4).

Summary

4:5-Benzothionaphthene (II) was obtained by the α-cyclization of β-naphthyl ω-dimethoxyethyl sulphide (I), and the hitherto unknown naphtho-(1′:8′-*bc*)-thiapyran (IV) by the *peri*-cyclization of α-naphthyl ω-dimethoxy-ethyl sulphide (III).

Naphthalene-1:5-dithiol was obtained in 85% yield by an improved method. Condensation of naphthalene-1:5 and 2:6-dithiols with two molecules of bromoacetaldehyde dimethyl acetal gave (VIII) and (XI). The former cyclized in the *peri*-positions to give "1:6-thiapyrene" (IX) which was orange in colour, and the latter cyclized in the α-positions to give 4:5, 5′:4′-dithionaphthene (XII), an isoster of chrysene which was colourless. Chrysene and (XII) gave similar absorption spectra, which were markedly different from the absorption spectrum of (IX).

The author is indebted to Dr. I. Berenblum for testing the carcinogenic properties of (IX) and (XII).

References

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