SULPHUR ISOSTERS OF CARCINOGENIC HYDROCARBONS

Part II. 6: 12-Dimethylbenzo(1: 2-*b*, 5: 4-*b'*)dithionaphthene and Thionaphtheno(4: 5: 4': 5')thionaphthene

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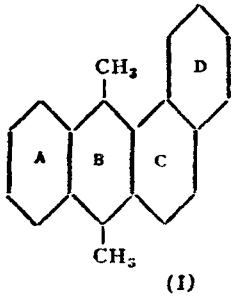
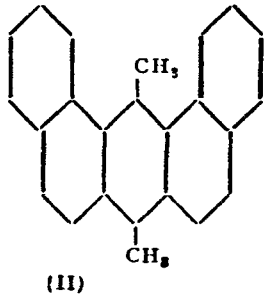
THE carcinogenic activity of polycyclic hydrocarbons has been related by Robinson[1] to the presence of an "activated phenanthrene bridge". With a view to study the significance of the phenanthrene bridge in chemical carcinogenesis, sulphur isosters of carcinogenic hydrocarbons in which an appropriate benzene ring is replaced by the isosteric thiophene nucleus were synthesized. The synthesis of 4: 9-dimethyl-2: 3-benzothiophanthrene (III) and 4: 9-dimethyl 2: 3: 5: 6-dibenzothiophanthrene (IV) which are sulphur isosters of 9: 10-dimethyl-1: 2-benzanthracene (I) and 9: 10-dimethyl-1: 2: 7: 8-dibenzanthracene (II), has been described in the previous communication.[2] Compound (III), where the phenanthrene bridge in (I) is removed by isosteric replacement of the benzene ring C, is inactive by subcutaneous injection in mice and weakly active on painting. It is highly



(I)



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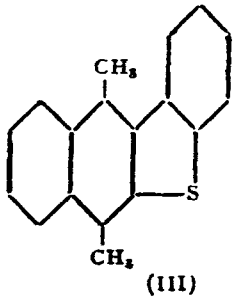

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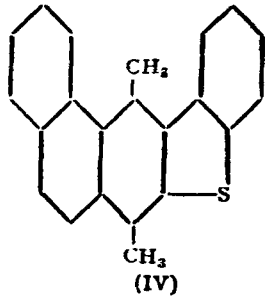
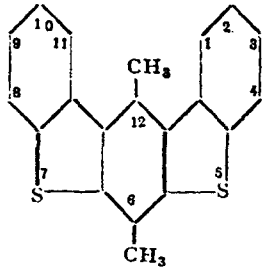


(IV)

significant that high activity again emerges in the benzo derivative (IV) where the phenanthrene double bond is once again introduced.

The present paper records the synthesis of the important key compound, 6: 12-dimethylbenzo(1 : 2-*b*, 5 : 4-*b*')dithionaphthene (V) which is the sulphur isoster of (II) where both the phenanthrene double bonds have been removed and the *meso*-positions blocked by methyl groups. The name and numbering of (V) follows from the corresponding benzodithiophene.[3] If (V) proves



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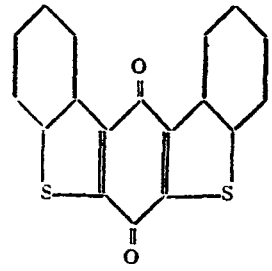
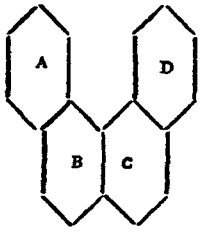


(VI)

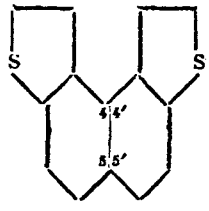
to be non-carcinogenic, the phenanthrene bridge hypothesis of Robinson will receive strong support.

The benzothionaphthene (V) was prepared from benzo (1 : 2-*b*, 5 : 4-*b*') dithionaphthene-6 : 12-quinone (VI) through the iodomethyl derivative according to Fieser and Hershberg.[4] The quinone (VI) was prepared according to Mayer[5] starting from thioisatin and *sym*-dichloroacetone.

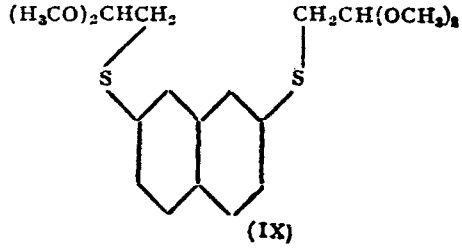
Synthesis of thiophene analogues of carcinogenic polycyclic hydrocarbons related to 1 : 2-benzanthracene have been described above and in the previous paper.[2] The study of carcinogenic activity of another important carcinogen, 3 : 4-benzphenanthrene (VII) has also been undertaken. Isosteric replacement of rings A and D in (VII) should not affect its carcinogenic activity whereas replacement of rings B and C should have profound effect. The synthesis of thionaphtheno(4 : 5, 4' : 5')thionaphthene (VIII), the thiophene analogue of (VII) obtained by replacement of rings A and D, is now described.



(VII)



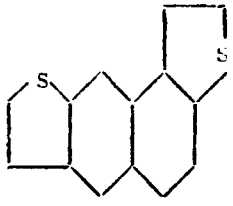
(VIII)



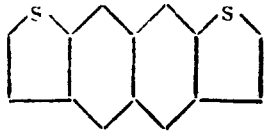
(IX)

2:7-Naphthalenedithiol was prepared in 76% yield by the reduction of 2:7-naphthalenedisulphonyl chloride by passing hydrogen chloride into a solution of the disulphonyl chloride and stannous chloride in absolute ethanol saturated with dry hydrogen chloride. It has been prepared previously by the reduction of the disulphonyl chloride with zinc and dilute sulphuric acid[6] (poor yields) or by reduction with zinc and acetic acid[7] (5% yield). 1:5-Naphthalenedithiol and 2:6-naphthalenedithiol have likewise been prepared in improved yields by the reduction of the corresponding disulphonyl chlorides with stannous chloride and ethanolic hydrogen chloride.[8] This method of reduction of disulphonyl chlorides to dithiols therefore appears to be more convenient than other methods of reduction.

Condensation of 2:7-naphthalenedithiol with two molecules of bromoacetaldehyde dimethyl acetal gave 2:7-*bis*-dimethoxyethylmercapto-naphthalene (IX). Ring-closure of (IX) was effected by treatment with phosphoric acid and phosphorus pentoxide. The cyclization product may be constituted as (VIII), (X) or (XI) depending on the direction of ring-closure of the thioglycolic-aldehyde dimethyl acetal side chains. Compounds (VIII), (X) and (XI) are dithiophene analogues of 3:4-benzphenanthrene, 1:2-benzanthracene and naphthacene respectively. Whereas naphthacene is coloured, the cyclization product from (IX) is colourless. In view of the favoured α-cyclization in the naphthalene series, the cyclization product is likely to be constituted as (VIII) rather than (X) or (XI). Further confirmation of this view was derived by comparison of the absorption spectra of the cyclization product with the spectra of 3:4-benzphenanthrene, 1:2-benzan-



(X)



(XI)

thracene and naphthacene.[9] The absorption spectrum of the cyclization product is widely divergent from naphthacene. It however shows greater resemblance to 3:4-benzphenanthrene as compared with 1:2-benzanthracene. The cyclization product from (IX) is therefore constituted as thionaphtheno-(4:5:4′:5′-) thionaphthene (VIII).

The carcinogenic activity of (V) and (VIII) will be examined in due course.

EXPERIMENTAL

6 : 12-Dimethylbenzo (1 : 2-b, 5 : 4-b') dithionaphthene (V)

A paste of the quinone (VI) (1·3 g.) in dry thiophene-free benzene (50 c.c.) was added to the Grignard reagent from magnesium (1·3 g.) and methyl iodide (5 c.c.) in dry ether (28 c.c.). It immediately dissolved giving a greenish yellow solution which was boiled under reflux for one hour. After the reaction was over, the mixture was cooled in ice and added gradually to a solution of hydriodic acid, sp. gr. 1·7 (16·8 c.c.) in methyl alcohol (27·4 c.c.) which was cooled in a freezing mixture. A yellow precipitate of the iodomethyl compound separated. The mixture was then diluted with glacial acetic acid (27 c.c.) and the precipitate was collected and dissolved in dioxan (60 c.c.). A mixture of stannous chloride (7·5 g.), concentrated hydrochloric acid (22 c.c.) and dioxan (40 c.c.) was added quickly and the mixture boiled gently for 15 minutes. Dioxan was removed under reduced pressure till the volume was about 30 c.c. The solution was cooled when a yellow product separated (0·382 g.), m.p. 184-88°, which after two crystallizations from benzene-alcohol gave yellow needles of the dithionaphthene (V), m.p. 189–90·5° (Found: C, 75·3; H, 4·5. $C_{20}H_{14}S_2$ requires C, 75·5; H, 4·4%). *sym*-Trinitrobenzene (35 mg.) and pure (V) (50 mg.) were boiled together in dry pure benzene. Concentration and cooling of the solution gave the *sym-trinitrobenzene derivative* as red needles, m.p. 190–1° (Found: C, 58·7; H, 3·0; N, 8·3. $C_{25}H_{17}N_3O_6S_2$ requires C, 58·7; H, 3·2; N, 7·9%).

2 : 7-Naphthalenedithiol

A mixture of dry sodium 2 : 7-naphthalenedisulphonate (20 g.) and phosphorus pentachloride (80 g.) was heated in an oil-bath at 140–50° for 4 hours. Phosphorus oxychloride was removed under reduced pressure and the residue was added to crushed ice. The crude disulphonyl chloride (19 g.) was crystallized from benzene in colourless plates (7·7 g.), m.p. 157°.

The disulphonyl chloride was converted to the dithiol by a modification of the method of Albenga and Corbellini[10] employed for the preparation of 1 : 5-naphthalenedithiol. Absolute alcohol (80 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 (40 g.) was added and the solution heated to boil. A suspension of the disulphonyl chloride (7·7 g.) in dry benzene (60 c.c.) was added in small portions. After each addition a vigorous reaction took place. Dry hydrogen chloride was passed throughout the experiment. The mixture was

refluxed further for 30 minutes and then distilled till 72 c.c. of the solvent distilled over. The residue gave lustrous plates of 2:7-naphthalenedithiol on cooling. The dithiol was collected in a sinter glass crucible and washed repeatedly with concentrated hydrochloric acid (total 50 c.c.) then with water and finally dried in vacuum over phosphorus pentoxide. The thiol (3·8 g., yield 76%) gave m.p. 179° (literature, 174°[8] and 181°[4]).

2:7-*bis*-*Dimethoxyethylmercaptonaphthalene* (*IX*)

2:7-Naphthalenedithiol (17 g.), sodium (5·1 g.), bromoacetaldehyde dimethyl acetal (40·7 g.), and absolute alcohol (200 c.c.) were refluxed on a water-bath for 3 hours. The acetal was isolated by means of ether when it gave a dark oil (25 g.; yield 77%). On crystallization from *n*-hexane, it gave pale yellow needles, m.p. 38° (Found: C, 58·6; H, 6·5. $C_{18}H_{24}O_4S_2$ requires C, 58·7; H, 6·5%).

Thionaphtheno (4:5:4′:5′) *thionaphthene* (*VIII*)

Phosphoric acid, sp. gr. 1·75 (15 c.c.) was added to a mixture of the acetal (IX) (3·0 g.) and phosphorus pentoxide (24 g.) and the mixture was immediately heated in an oil-bath kept at 150–60° for 5 minutes and then diluted into crushed ice. The product was collected and extracted with hot benzene. The benzene extract was washed with aqueous sodium hydroxide, dried and the solvent removed. The yellow crystalline residue (1·29 g.) was redissolved in benzene and the solution passed through activated alumina. The product gave a uniform chromatogram and showed blue fluorescence in ultraviolet light. The chromatographed product was further purified through the picrate. Decomposition of the picrate with 1% ammonia gave a pale yellow product (0·55 g., yield 29%), m.p. 162–63°. After sublimation at 180–200°/10 mm. and crystallization from *n*-hexane, the thionaphthenothionaphthene gave colourless plates, m.p. 163° (Found: C, 69·8; H, 3·5. $C_{11}H_8S_2$ requires C, 70·0; H, 3·3%). The *picrate* gave orange needles from alcohol, m.p. 185° (Found: N, 9·1. $C_{20}H_{11}N_3O_7S_2$ requires N, 9·0%).

SUMMARY

With the view to study the significance of the 9:10-phenanthrene double bond (" phenanthrene bridge ") in 9:10-dimethyl-1:2:7:8-dibenzanthracene (II), 6:12-dimethylbenzo(1:2-*b*, 5:4-*b*′)dithionaphthene (V) was prepared where both the phenanthrene bridges in (II) are removed by isosteric replacement with thiophene rings and the *meso*-positions are blocked by methyl groups. Compound (V) should prove noncarcinogenic.

2:7-Dimethoxyethylmercaptonaphthalene (IX) on cyclization gave thionaphtheno(4:5:4′:5′-)thionaphthene (VIII). The constitution (VIII)

follows from the favoured α-cyclization in the naphthalene series and the similarity of its absorption spectrum with that of 3:4-benzphenanthrene.

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