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CARCINOGENESIS BY THIOPHENE ISOSTERS OF POLYCYCLIC HYDROCARBONS

SYNTHESIS OF CONDENSED THIOPHENES

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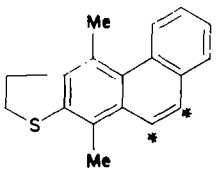
Abstract—Contributions by the author extending over the last 15 years on two related topics have been reviewed: (1) Carcinogenesis by thiophene isosters of polycyclic hydrocarbons in connexion with the study of the rôle of the 9,10-double bond in phenanthrene (K region) and (2) Synthesis of condensed thiophenes and thiapyrans. The survey also includes a considerable amount of unpublished work.

Thiophene isosters of polycyclic carcinogenic hydrocarbons

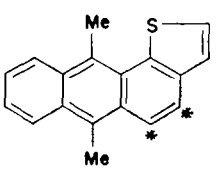
CHEMICAL carcinogenesis has been extensively investigated and several reviews on the subject are available.[1] Among the large number of chemical carcinogens, the polycyclic hydrocarbons are the most systematically studied in view of their structural relationship to the naturally occurring compounds such as, the steroids on the one hand, and their association with certain forms of occupational cancer on the other. Series of closely related hydrocarbons have been prepared with the view to study the relationship between chemical structure and biological activity. Majority of polycyclic hydrocarbons, that have proved carcinogenic, are phenanthrene derivatives suitably substituted by alkyl groups or with fused aryl ring attached to phenanthrene. Many heterocyclic analogues of these carcinogenic hydrocarbons such as, acridine, carbazoles and thiophene derivatives have also proved to be carcinogenic.[1] These facts led Robinson to suggest that the essential structural feature for carcinogenicity in the polycyclic hydrocarbons may be an activated phenanthrene bridge (the 9,10-double bond in phenanthrene shown by asterisks in formulae) which needs to be unsubstituted.[2] With this end in view, Robinson and Tilak initiated a programme of synthesis of thiophene isosters of carcinogenic hydrocarbons, wherein the sulphur atom in the thiophene ring replaced the key phenanthrene bridge.[3]

In this connexion, compounds III, IV and IVA were prepared.[3,4] As against the activity of I and II, prepared earlier[5,6] III was only slightly active when painted on mice and inactive when injected subcutaneously.[1b] The inactivity of III was

[1] (*a*) A. Haddow, *Brit. Med. Bull.* **4**, 314, 331 (1947).
(*b*) J. L. Hartwell, *Survey of Compounds Tested for Carcinogenic Activity*. U.S. Public Health Service (1951).
(*c*) G. M. Badger, *Roy. Aust. Chem. Inst. J. & Proc.* **17**, 14 (1950).
(*d*) Ng. Ph. Buu-Hoi, *Chem. Progr.* **13**, 23 (1952).
(*e*) G. M. Badger, *Advances in Cancer Research* Vol. II, pp. 73–127. Academic Press, New York (1954).
[2] R. Robinson, *Brit. Med. J.* **1**, 945 (1946).
[3] B. D. Tilak, D. Phil. Thesis Oxford University (1946).
[4] B. D. Tilak, *Proc. Indian Acad. Sci.* **33A**, 131 (1951).
[5] R. B. Sandin and L. F. Fieser, *J. Amer. Chem. Soc.* **62**, 3102 (1940).
[6] E. B. Hershberg and L. F. Fieser, *J. Amer. Chem. Soc.* **63**, 2563 (1941).



I



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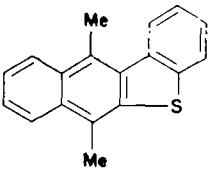
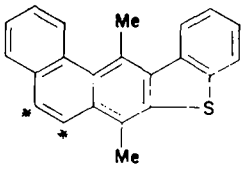
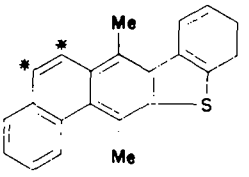


III

attributed to the absence of the phenanthrene bridge, since high activity again emerged in the case of IV and IVA which contain a phenanthrene bridge.



IV



IV a

While the above data was being collected, Pullman *et al.* and Coulson approached the problem from quantum mechanical considerations. Summaries of their conclusions are available in recent literature.[7,8] Since the first step in carcinogenesis involves a reaction of the carcinogen and a cellular receiver probably of an electrophilic nature, Pullmann[7] postulated that the "K-region" should be sufficiently active and that the "L-region" (meso positions in anthracene residue) should be inactive (by substitution, e.g. by methyl groups). The activities of these centres were expressed in terms of electrical indices calculated by Pullmann on the basis of bond localization energies. There are, however, certain exceptions which are difficult to explain on the basis of the Pullmann hypothesis.

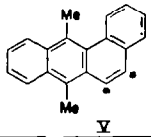
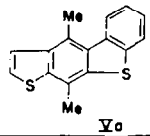
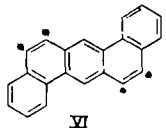
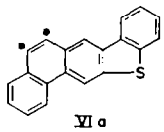
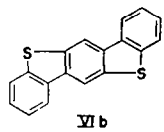
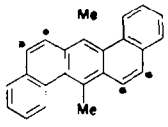
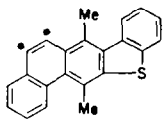
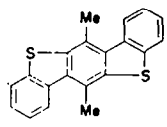
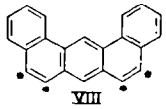
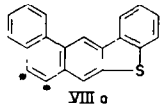
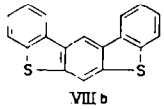
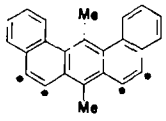
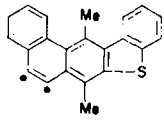
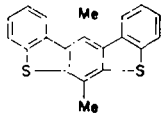
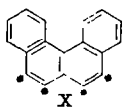
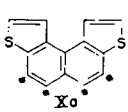
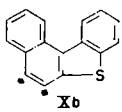
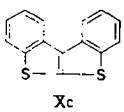
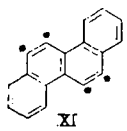
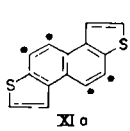
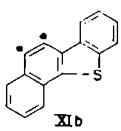
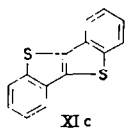
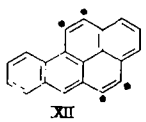
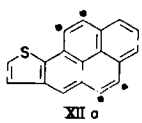
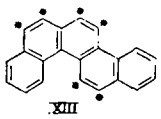
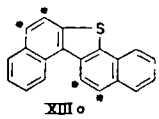
The interaction at the phenanthrene bridge in the metabolism of 1:2,5:6-dibenzanthracene has been demonstrated by Heidelberger.[9] This work indicates that the phenanthrene bridge is involved in carcinogenesis by 1:2,5:6-dibenzanthracene.

The synthesis of key thiosters of carcinogenic hydrocarbons wherein the "K-region" is replaced by isosteric substitution by means of thiophene has been continued by the author.[4] Thus thiosters of the following carcinogens were prepared: 9,10-dimethyl-1:2-benzanthracene (V), 1:2,5:6-dibenzanthracene (VI), 9,10-dimethyl-1:2,5:6-dibenzanthracene (VII), 1:2,7:8-dibenzanthracene (VIII), 9,10-dimethyl-1:2,7:8-dibenzanthracene (IX), 3:4-benzphenanthrene (X), chrysene (XI), 3:4-benzpyrene (XII) and 1:2,5:6-dibenzphenanthrene (XIII). The phenanthrene-bridges referred to hereafter as PB/s are shown by asterisks and the thiosters synthesized are shown alongside with the hydrocarbons in Chart I.

Thiosters of 9,10-*dimethyl*-1:1-*benzanthracene* (V). The carcinogenic activity of the thiosters I, II and III has been discussed earlier. Isoster VA has also been prepared,[10] but could not be tested for want of material.

[7] A. Pullmann and B. Pullmann, *Advances in Cancer Research* Vol. III, p. 1711, Academic Press, New York (1955).
[8] C. A. Coulson, *Advances in Cancer Research* Vol. I, pp. 1–56, Academic Press, New York (1953).
[9] P. M. Bhargava, H. I. Halder and C. Heidelberger, *J. Amer. Chem. Soc.* **77**, 2877 (1955); **78**, 3671 (1956).
[10] V. V. Ghaisas and B. D. Tilak, *J. Sci. Ind. Res., India* **14B**, 11 (1955).

Chart I

Carcinogenic hydrocarbons	Thiosters
 V	I II III  Va
 VI	 VI a  VI b
 VII	 IV a  VII b
 VIII	 VIII a  VIII b
 IX	 IV  IX b
 X	 Xa  Xb  Xc
 XI	 XI a  XI b  XI c
 XII	 XII a
 XIII	 XIII a

Thiosters of 1:2,5:6-*dibenzanthracene* (VI). In compound VIB both the PBs are replaced by sulphur[11] and the compound has proved inactive.[12] Compound VIA, wherein only one of the two PBs in VI is replaced, has been synthesized very recently, and remains to be tested.[13]

Thiosters of 9,10-*dimethyl*-1:2,5:6-*dibenzanthracene* (VII). The two PBs in VII have been replaced stepwise as in IVA[3,4] and VIIB.[10] Compound IVA is a much more powerful carcinogen than VII[1b] and the high activity was attributed to a single activated PB instead of two competitive PBs as in VII.[4] The key thioster VIIB, wherein both the PBs are removed, however, proved highly active contrary to the expectation that it would be inactive.[12]

Thioster of 1:2,7:8-*dibenzanthracene* (VIII). Thiosters VIIIA[13] and VIIIB[14] have been recently synthesized wherein the two PBs in VIII have been removed stepwise. These compounds have yet to be tested.

Thiosters of 9,10-*dimethyl*-1:2,7:8-*dibenzanthracene* (IX). When one of the two PBs in IX was replaced, a highly active carcinogen IV resulted as expected.[4] However, the key thioster IXB, wherein both the PBs were removed[15], also proved to be highly carcinogenic, contrary to its expected inactivity.[12]

Thiosters of 3:4-*benzphenanthrene* (X). All the three thiosters XA,[15] XB,[16,17] and XC[18] of this weakly active carcinogen X have proved inactive.[1b,12]

Thiosters of chrysene (XI). Conflicting reports have appeared as regards the carcinogenic activity of chrysene.[1b] Out of the three thiosters XIA,[20] XIB[16] and XIC,[19] the key compound XIC, wherein both the PBs are removed, has proved noncarcinogenic.[12] Compounds XIA and XIB are also inactive.[1b,12]

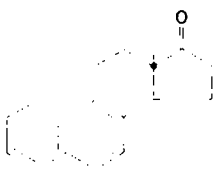
Thiosters of 3:4-*benzpyrene* (XII). This thioster XIIA[21] in which the two K-regions of 3:4-benzpyrene XII are unaffected is under study for its carcinogenic activity.

Thiosters of 1:2,5:6-*dibenzphenanthrene* (XIII). As against the weak carcinogenic activity of XIII[1b] its thioster 1:2,5:6-dibenzo-9-thiafluorene (XIIIA)[17] has given a highly toxic initial reaction when given subcutaneously to mice.[12a] The test is still in progress.

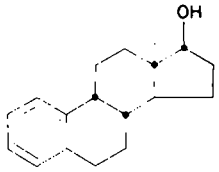
Thiosters of phenolic steroids. Compounds XIVA[22] and XVA[23] which are thiosters of 3-desoxyequilenin (XIV) and 3-desoxyisoestradiol (XV), were synthesized as a preliminary step in the synthesis of B-nor-6-thiaequilenin (XIVB) and B-nor-6-thiaestradiol (XVB). It is of interest to compare the carcinogenic and estrogenic properties of these thiosters and the corresponding natural steroids.

In conclusion it may be said that the interrelation between carcinogenicity and the structure of polycyclic hydrocarbons and their thiosters does not appear to be simple.

[11] D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res., India* **17B**, 260 (1958).
[12] K. J. Ranadive and S. S. Waravdekar, *J. Nat. Cancer Inst.* **18**, 555 (1957).
[12a] K. J. Ranadive and S. S. Waravdekar, Private communication.
[13] G. N. Pillai and B. D. Tilak, Unpublished work.
[14] L. J. Pandya, G. N. Pillai and B. D. Tilak, *J. Sci. Ind. Res., India* **18B**, 198 (1959).
[15] V. V. Ghaisas, K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci.* **37A**, 114 (1953).
[16] K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci.* **37A**, 564 (1953).
[17] K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci.* **38A**, 271 (1953).
[18] R. B. Mitra, L. J. Pandya and B. D. Tilak, *J. Sci. Ind. Res., India* **16B**, 348 (1957).
[19] V. V. Ghaisas and B. D. Tilak, *J. Sci. Ind. Res., India* **16B**, 345 (1957).
[20] B. D. Tilak, *Proc. Indian. Acad. Sci.* **33A**, 71 (1951).
[21] L. J. Pandya and B. D. Tilak, *Chem. & Ind.* 981 (1958).
[22] R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res., India* **14B**, 132 (1955); **15B**, 497 (1956).
[23] R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. India* **15B**, 573 (1956).



XIV



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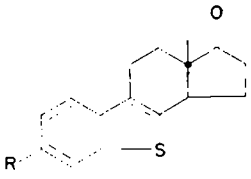
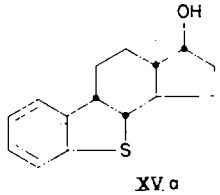
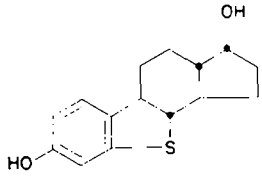


XIV a, R = H

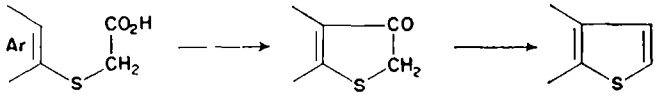
XIV b, R = OH



XV a



XV b



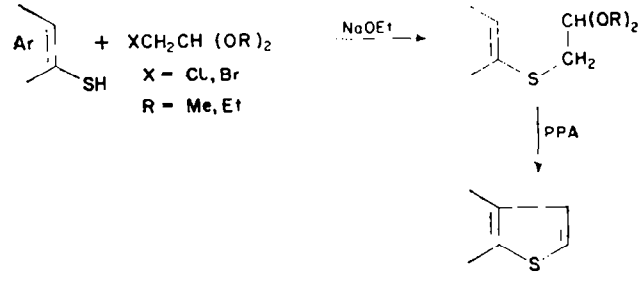
XVI XVII XVIII

opportunities for contributions in the field of condensed thiophenes. The present paper gives a summary of the several new and general methods for the synthesis of condensed thiophenes developed by the author.

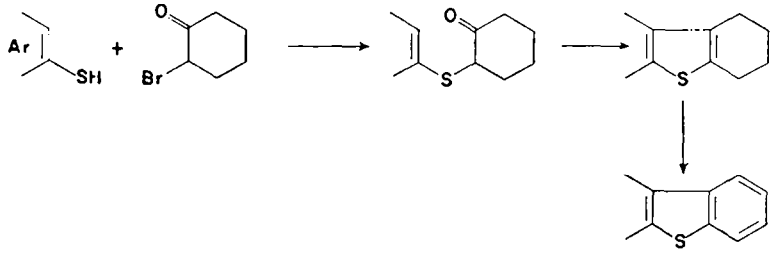
Synthesis of condensed thiophenes from arylthiols

One or more thiophene, thiapyran, thionaphthene and naphthothiophene ring systems were fused to an aromatic residue by starting from aryl mono- and di-thiols on the one hand and halogenoacetaldehyde dialkyl acetals[3,25] and α-halogenocyclic ketones (2-bromocyclohexanone[27] and 2-bromo-1-tetralone[17]) on the other. These approaches may be summarized as follows:

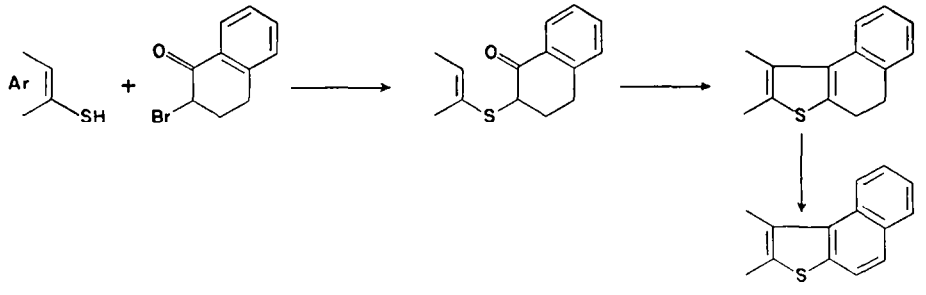
Method I: *Fusion of one or more thiophene or thiapyran rings to an aryl residue*[3,25]



Method II: *Fusion of benzothiophene ring system to an aryl residue*[27]



Method III: *Fusion of a naphthothiophene ring system to an aryl residue*[17]



[27] K. Rabindran and B. D. Tilak, *Curr. Sci.* **20**, 207 (1951); *Proc. Indian Acad. Sci.* **36A**, 411 (1952).

TABLE 1. CONDENSED THIOPHENES FROM ARYL THIOLS AND HALOGENOACETALDEHYDE-DIALKYL ACETALS (Method I)*

No.	Aryl ω-dimethoxyethyl sulphide	% Yield from thiol	Condensed thiophenes	% Yield from sulphide	Ref.
1	Phenyl ω-dimethoxyethyl sulphide	76	Thionaphthene	37	3, 25
				89	28
2	Phenyl ω-diethoxyethyl sulphide	—	Thionaphthene	32	3, 25
3	*p*-Tolyl ω-dimethoxyethyl sulphide	65	5-Methylthionaphthene	48	29
4	*m*-Tolyl ω-dimethoxyethyl sulphide	69		42	29
			6-Methylthionaphthene	78	28
5	*o*-Tolyl ω-dimethoxyethyl sulphide	69	7-Methylthionaphthene	53	29
6	*p*-Chlorophenyl ω-dimethoxy--ethyl sulphide	69	5-Chlorothionaphthene	43	29
7	*m*-Chlorophenyl ω-dimethoxy-ethyl sulphide	65	6-Chlorothionaphthene	32	29
			4-Chlorothionaphthene		29a
8	*o*-Chlorophenyl ω-dimethoxyethyl sulphide	62	7-Chlorothionaphthene	40	29
				72	28
9	*o*-Bromophenyl ω-dimethoxyethyl sulphide	78	7-Bromothionaphthene	75 (39)	30
10	*p*-Bromophenyl ω-dimethoxyethyl sulphide	72	5-Bromothionapthene	13	30
11	*p*-Nitrophenyl ω-dimethoxyethyl sulphide	68	5-Nitrothionaphthene	12	30
12	*o*-Nitrophenyl ω-dimethoxyethyl sulphide		Did not cyclize		30
13	*p*-Methoxyphenyl ω-dimethoxyethyl sulphide	70	5-Methoxythio-naphthene	low	31
14	*m*-Methoxyphenyl ω-dimethoxyethyl sulphide	74		crude	
			6-Methoxythio-naphthene	62	31
15	*o*-Methoxyphenyl ω-dimethoxyethyl sulphide	82	7-Methoxythio-naphthene	18	31
16	*p*-Ethoxyphenyl ω-dimethoxyethyl sulphide	85	5-Ethoxythionaphthene	15	31
17	3-Methoxy-4-methylphenyl ω-dimethoxyethyl sulphide	84	6-Methoxy-5-methyl-thionaphthene	64	31

* Where two yields are quoted for the same compound, the yield in brackets refers to yield of the purer compound. In all other cases, the yield figure relates to the pure compound.

[18] K. Rabindran and B. D. Tilak, *Curr. Sci.* **20**, 205 (1951).
[19] A. V. Sunthankar and B. D. Tilak, *Proc. Indian. Acad. Sci.* **32A**, 396 (1950).
[19a] C. Hansch and B. Schmidhalter, *J. Org. Chem.* **20**, 1056 (1955).
[20] K. Rabindran, A. V. Sunthankar and B. D. Tilak, *Proc. Indian Acad. Sci.* **36A**, 405 (1952).
[21] A. V. Sunthankar and B. D. Tilak, *Proc. Indian Acad. Sci.* **33A**, 35 (1951).

TABLE 1 (*contd.*)

No.	Aryl ω-dimethoxyethyl sulphide	% Yield from thiol	Condensed thiophenes	% Yield from sulphide	Ref.
18	β-Naphthyl ω-dimethoxyethyl sulphide	40	4:5-Benzothionaphthene	54	20
19	α-Naphthyl ω-Dimethoxyethyl sulphide	69	Naphtho-(1′,8′-*bc*)-thiapyran (8%) and 6:7-benzothionaphthene (92%)	53 (Mixtr.)	20 32
20	8-Chloro-l-naphthyl ω-dimethoxyethyl sulphide	70	3′-Chlorobenzo-(1′:2′, 6:7)-thionaphthene	82 Crude	33
21	2-Chloro-l-naphthyl ω-dimethoxyethyl sulphide	72	9-Chloronaphtho-(1′,8′-*bc*) thiapyran.	11	32,33
22	3-Phenanthryl ω-dimethoxyethyl sulphide		7:8-Benzothiophanthrene	36	34
23	3-Thienyl ω-dimethoxyethyl sulphide	66	Thieno-(3,2-*b*) thiophene	18	35,36
24	2-Thienyl ω-dimethoxyethyl sulphide	73	Thieno-(2,3-*b*) thiophene	46 (18)	35,36
25	ω-Dimethoxyethyl 2-thionaphthenyl sulphide	70	Thieno-(2,3-*b*)-thionaphthene	48	18
26	1,2-Bis-ω-dimethoxyethyl-mercaptobenzene	70	Benzo-(2,1-*b*,3,4-*b*′)-dithiophene	Poor	11
27	4-Bromo-1,2-bis-ω-dimethoxyethylmercaptobenzene	48	4-Bromobenzo-(2,1-*b*,3,4-*b*′) dithiophene	7	11
28	1,3-Bis-ω-dimethoxyethyl-mercaptobenzene	66	Benzo-(1,2-*b*,5,4-*b*′)-dithiophene (41%) + Benzo-(1,2-*b*,3,4-*b*′)-dithiophene (59%)	50 (Mixtr.)	37
29	1-Chloro-2,4-bis-ω-dimethoxyethylmercaptobenzene	72	8-Chlorobenzo-(1,2-*b*,3,4-*b*′)-dithiophene	45	37
30	1,4-Bis-ω-dimethoxyethyl-mercaptobenzene	52	Benzo-(1,2-*b*,4,3-*b*′)-dithiophene	32 (23)	38
31	1,4-Dichloro-2,5-bis-ω-dimethoxyethylmercaptobenzene	83 crude	4,8-Dichlorobenzo-(1,2-*b*,4,5-*b*′)-dithiophene	54	38
32	1,3-Di-(ω-dimethoxyethyl-mercapto)-naphthalene	88	Naphtho-(1,2-*b*,3,4-*b*′)-dithiophene, m.p. 169°	80	39

[33] H. S. Desai, D. S. Rao and B. D. Tilak, *Chem. & Ind.* 464 (1957).
[34] V. K. Dikshit and B. D. Tilak, *Proc. Indian Acad. Sci.* **33A**, 78 (1951).
[35] B. D. Tilak, *Proc. Indian Acad. Sci.* **33A**, 85 (1951).
[36] V. V. Ghaisas and B. D. Tilak, *Curr. Sci.* **22**, 184 (1953).
[37] V. V. Ghaisas and B. D. Tilak, *Proc. Indian Acad. Sci.* **39A**, 14 (1954).
[38] D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res., India* **13B**, 829 (1954).
[39] D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res., India* **16B**, 65 (1957).
[40] H. S. Desai and B. D. Tilak, Unpublished work

TABLE 1 (*contd.*)

No.	Aryl ω-dimethoxyethyl sulphide	% Yield from thiol	Condensed thiophenes	% Yield from sulphide	Ref.
33	1,4-Di-(ω-dimethoxyethyl-mercapto)-naphthalene	80	Naphtho-(1,2-*b*,4,3-*b'*) dithiophene m.p. 134°	8	39
34	1,5-Di-(ω-dimethoxyethyl-mercapto)-naphthalene	38	1,6-Dithiopyrene Naphtho-(1′,8′-*bc*, 5′,4′-*b'c'*)-dithiapyran	7	20,39
35	2,6-Di-(ω-dimethoxyethyl-mercapto)-naphthalene	51	Naphtho-(2,1-*b*,6,5-*b'*)-dithiophene	20	20
36	2,7-Di-(ω-dimethoxyethyl-mercapto)-naphthalene	77	Naphtho-(2,1-*b*,7,8-*b'*)-dithiophene	29	15
37	4-ω-Dimethoxyethyldiphenyl sulphide	78	5-Phenylthionaphthene m.p. 100°	79	40
38	4,4′-Di-(ω-dimethoxyethyl-mercapto)-diphenyl ether	42	5,5′-Dithionaphthenyl ether, m.p. 93°	10	40

The condensed thiophenes and thiapyrans synthesized by methods I, II and III are tabulated in Tables 1, 2 and 3 respectively which include reference to their preparation. Melting points and boiling points of hitherto unreported condensed thiophenes are also included in Tables 1–3 and other tables that follow.

Scope and limitation of Methods I, II *and* III. The general applicability of the methods for the synthesis of condensed thiophenes will be obvious from the large number of compounds synthesized (Tables 1–3). The only requisite for fusing a thiophene or a condensed thiophene ring system appear to be an aryl thiol with free *o* or *peri* position to enable cyclization of the thioglycolic-acetaldehyde dialkyl acetal side chain in Method I or the cyclodehydration of the 2-arylmercapto-cycloalkanones in Methods II and III.

The scope of Method I in the substituted thionaphthenes appears to be largely limited to 5-, 6-, and 7- substituted derivatives[4] although in one instance, 4-chloro-thionaphthene[29,29a] has also been prepared by this method. It may be mentioned that prior to the developement of Method I, only very few substituted thionaphthenes with substituents in the benzene half of the molecule were known. The latter type of thionaphthenes where the substituent is Cl, Br, O Me, Me, Et are now readily synthesizable by Method I. When the substituent was a nitro group, the yield of the thionaphthene was very low.[30] Other thionaphthenes containing substituents such as, hydroxy,[31] amino,[30] cyano[41] and carboxy[42] groups were then synthesized, starting from suitably substituted thionaphthenes prepared by Method I. Starting with aryl dithiols two thiophene rings have been fused to a benzene or naphthalene ring. In the case of α-thionaphthol, the end products were 6:7-benzothionaphthene and naphtho-(1′:8′-*bc*)-thiapyran.[32] Naphthalene-1,5-dithiol likewise gave a bis-thiapyran.[20,39] With the exception of a recently described thiapyran,[42] these compounds appear to be

[40] L. J. Pandya, D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res., India* **18B**, 516 (1959).
[41] R. B. Mitra, K. Rabindran and B. D. Tilak, *J. Sci. Ind. Res., India* **15B**, 627 (1956).
[42] A. G. Anderson, Jr., W. F. Harrison, R. G. Anderson and A. G. Osborne, *J. Amer. Chem. Soc.* **81**, 1255 (1959).

the only two examples of aromatic thiapyrans. Both are deeper in colour than the corresponding thiophenes and give characteristic black coloured picrates as against yellow, orange or red coloured picrates given by condensed thiophenes. The structure of the bis-thiapyran from naphthalene-1,5-dithiol suggested by the author has been questioned by Banfield *et al.*[43] However, since desulphurization of the product gave 1,5-diethylnaphthalene, the structure suggested by the author is undoubtedly correct.[39] It is, however, interesting to record that cyclization of 1,5-di-acetonyl-mercaptonaphthalene gave exclusively 3,8-dimethyl-(6,7:7′,6′)-dithionaphthene, no thiapyran being detected. Similarly naphthalene-1,4-dithiol and naphthalene-1,3-dithiol also led to naphtho-(1:2-*b*,4,3-*b*′)-dithiophene and naphtho-(1:2-*b*,3:4-*b*′)-dithiophene respectively (Table 1). The structure of the latter compounds was proved by desulphurization and identification of the corresponding diethylnaphthalenes.[39] Method I is applicable to thiols derived from both, homocyclic as well as heterocyclic aromatic compounds such as, thiophene and thionaphthene, although ω-dimethoxy-ethyl 2-pyridyl sulphide failed to cyclize on treatment with PPA as discussed later.[29,49] In majority of cases the method has led to condensed thiophenes of unambiguous structure, but where more than one possibility exists as regards the direction of cyclization of the sulphide side chain, the structures of the resulting condensed thiophenes have been proved either by suitable degradations (desulphurization, oxidation, etc.) or by unambiguous synthesis (e.g. by blocking alternative cyclization positions by means of chlorine and dechlorination at a later stage).

Cyclization of the sulphide chain carrying the acetal group is best effected by the action of polyphosphoric acid (freshly prepared by mixing P_2O_5 and H_3PO_4) under reduced pressure or at atmospheric pressure in the presence or absence of boiling solvents such as, benzene, chlorobenzene or *o*-dichlorobenzene. Banfield *et al.*[43] have have used stannic chloride in chlorobenzene for the cyclization of acetals but they also found that PPA gave higher yields of the condensed thiophenes.

A series of condensed thionaphthenes and benzothionaphthenes have become available as a result of Methods II and III. Several of these compounds are of interest in the study of the chemical carcinogenesis discussed earlier in this paper. Whereas in Method I, thiophene or thiapyran rings are fused at the end of an aromatic ring system, in Methods II and III, benzothiophene or naphthothiophene rings are so fused. As against two steps involved in Method I, Methods II and III require three steps (condensation, cyclodehydration and dehydrogenation) for the conversion of arylthiols to condensed thiophenes. The yields in all the three steps are generally satisfactory. The scope and limitations of these methods are nearly the same as those for Method I. However, as against Method I, α-thionaphthol and naphthalene-1,5-dithiols did not lead to condensed thiapyrans[16,39] but to condensed thiophenes. The problems in structure determination were the same as in Method I and were dealt with similarly. As against the stability of halogenoacetaldehyde dialkyl acetals, 2-bromo-cyclohexanone is unstable and has to be freshly prepared and immediately used for condensation with arylthiols. This condensation is effected in aqueous alkali or in ethanolic sodium ethoxide. An alternative method consists in the use of pyridine

[43] J. E. Banfield, W. Davies, B. C. Ennis, S. Middleton and Q. N. Porter, *J. Chem. Soc.* 2607 (1956).
[44] M. K. Bhattacharjee and B. D. Tilak, Unpublished work.
[45] K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci.* 37A, 557 (1953).
[46] L. J. Pandya, Ph.D. (Tech.) Thesis University of Bombay (1959).
[47] G. R. N. Sastry and B. D. Tilak, Unpublished work.

TABLE 2. CONDENSED THIOPHENES FROM ARYL THIOLS AND BROMOCYCLOHEXANONE
(Method II)

No.	2-Arylmercaptocyclo-hexanones	% Yield from thiol	Reduced condensed thiophenes	% Yield from 2-aryl-mercapto cyclo-hexanone	Condensed thiophene	% Yield from reduced condensed thiophene	Ref.
1	2-Phenylmercaptocyclo-hexanones	77	1,2,3,4-Tetrahydrodibenzo-thiophene	74	Dibenzothiophene	91	27
2	2-(4′-Methylphenylmercapto)-cyclohexanone	68	2-Methyl-6,7,8,9-tetrahydro-dibenzothiophene	60	2-Methyldibenzothiophene	46	27
3	2-(3′Methylphenylmercapto)-cyclohexanone	80	3-Methyl-6,7,8,9-tetrahydro-thiophene	78	3-Methyldibenzothiophene	79	27
4	2-(2′-Methylphenylmercapto)-cyclohexanone	85	4-Methyl-6,7,8,9-tetrahydro-dibenzothiophene	62	4-Methyldibenzothiophene	51	27
5	2-(4′-Methoxyphenyl-mercapto)-cyclohexanone	75	2-Methoxy-6,7,8,9-tetrahydro-dibenzothiophene	low	—	—	27
6	2-(3′-Methoxyphenyl-mercapto)-cyclohexanone	50	3-Methoxy-6,7,8,9-tetrahydro-dibenzothiophene, b.p. 155° (bath temp)/0·5 mm	70	3-Methoxydibenzo-thiophene, m.p. 85°	30	44
7	2-(2′-Methoxyphenyl-mercapto)-cyclohexanone	77	4-Methoxy-6,7,8,9-tetrahydro-dibenzothiophene	47	4-Methoxydibenzo-thiophene	30	27
8	2-(4′-Nitrophenylmercapto)-cyclohexanone	92	Did not cyclize	—	—	—	27
9	2-(2′-Chlorophenyl-mercapto)-cyclohexanone	75	4-Chloro-6,7,8,9-tetrahydro-dibenzothiophene	56	4-Chlorodibenzothiophene	75	41
10	2-α-Naphthylmercapto-cyclohexanone	87	1,2-Benzo-5,6,7,8-tetrahydro-thiafluorene	70	1,2-Benzo-9-thiafluorene	90	16
11	2-(8′-Chloro-1′-naphthyl-mercapto)-cyclohexanone	99	1,2-(3′Chloro-2′,1′-benzo)-5,6,7,8-tetrahydro-9-thiafluorene	66	Se 1:2-Benzo-9-thiafluorene NBS 1,2-(3′-chloro-2′,1′-benzo)-9-thiafluorene	87	16 45
12	2-(β-Naphthylmercapto)-cyclohexanone	93	3,4-Benzo-5,6,7,8-tetrahydro-9-thiafluorene, P_2O_5 P_2O_5 in boiling benzene Vacuum distillation	38 82 47	3,4-Benzo-9-thiafluorene	Se → 100 NBS → 65	16

13	2-(3′-Thienylmercapto)-cyclohexanone		5,6,7,8-Tetrahydrothieno-(3,2-*b*)-thionaphthene		Thieno-(3,2-*b*)-thionaphthene	80	35,36
14	2-(2′-Thienylmercapto)-cyclohexanone	81	4,5,6,7-Tetrahydrothieno-(2,3-*b*)-thionaphthene	44	Thieno-(2,3-*b*)-thionaphthene		35,36 46
15	2-(3′-Thionaphthenyl-mercapto)-cyclohexanone		1,2,3,4-Tetrahydrothionaphtheno-(3,2-*b*)-thionaphthene		Thionaphtheno-(3,2-*b*)-thionaphthene		19
16	2-(2′-Thionaphthenyl-mercapto)-cyclohexanone	95	1,2,3,4-Tetrahydrothionaphtheno-(2,3-*b*)-thionaphthene	70	Thionaphtheno-(2,3-*b*)-thionaphthene	61	18
17	*m*-Di-(2-oxo-cyclohexyl-mercapto)-benzene	55	1,2,3,4,6,7,8,9-Octahydro benzo-(1,2-*b*, 3,4-*b*′)-dithionaphthene	56	Benzo-(1,2-*b*, 3,4-*b*′)-dithionaphthene	46	37
18	1-Chloro-2,4-di-(2′-oxo-cyclohexylmercapto)-benzene	55	11-Chloro-1,2,3,4,6,7,8,9-octahydrobenzo-(1,2-*b*, 3,4-*b*′)-dithionaphthene	46	Benzo-(1,2-*b*,3,4′-*b*′)-dithionaphthene		37
19	*p*-Di-(2-oxo-cyclohexyl-mercapto)-benzene	73	A mixture of 1,2,3,4,7,8,9,10-octahydrobenzo-(1,2-*b*, 4,5-*b*′) dithionaphthene (9%) and 1,2,3,4,9,10,11,12-Octahydro-benzo-(1,2-*b*, 4,3-*b*′)-dithionaphthene (10%)	64 (Mixture)	Benzo-(1,2-*b*,4,5-*b*′)-dithionaphthene (24%) and Benzo-(1,2-*b*, 4,3-*b*′)-dithionaphthene (33%)		11
20	1,4-Dichloro-2,5-di-(2-oxo-cyclohexylmercapto)-benzene	53	6,12-Dichloro-1,2,3,4,7,8,9,10-octahydrobenzo-(1,2-*b*, 4,5-*b*′)-dithionaphthene	43	Benzo-(1,2-*b*, 4,5-*b*′)-dithionaphthene	44	11
21	1,3-Di-(2-oxo-cyclohexyl-mercapto)-naphthalene	87	1,2,3,4,6,7,8,9-Octahydronaphtho (2,1-*b*, 4,3-*b*′)-dithionaphthene. m.p. 152°·5	72	Naphtho-(2,1-*b* 4,3-*b*′)-dithionaphthene m.p. 221°	92	39
22	1,4-Di-(2-oxo-cyclohexyl-mercapto)-naphthalene		1,2,3,4,5,6,7,8-Octahydro-naphtho-(1,2-*b*, 4,3-*b*′)-dithionaphthene, m.p. 225·5°		Naphtho-(1,2-*b*, 4,3-*b*′)-dithionaphthene, m.p. 215°		39
23	1,5-Di-(2-oxo-cyclohexyl-mercapto)-naphthalene, m.p. 194°	94	1,2,3,4,8,9,10,11-Octahydro-naphtho-(1,2-*b*, 5,6-*b*′)-dithionaphthene, m.p. 325°	44	Naphtho-(1,2-*b*, 5,6-*b*′)-dithionaphthene. m.p. > 360°	80	39

TABLE 3.— CONDENSED THIOPHENES FROM ARYL THIOLS AND 2-BROMO-1-TETRALONE

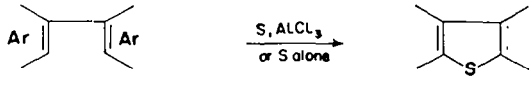
No.	2-Arylmercapto-1-tetralones	% Yield from thiol	Dihydro derivatives of condensed thiophenes	% Yield from 2-aryl mercapto-1-tetralone	Condensed thiophenes	% Yield from the dihydro derivative	Ref.
1	2-Phenylmercapto-1-tetralone	83	1,2-Dihydro-3,4-benzo-9-thiafluorene	94	3,4-Benzo-9-thiafluorene	95	17
2	2-(2′-Naphthylmercapto)-1-tetralone	88	1,2-Dihydro-3,4,5,6-dibenzo-9-thiafluorene	97	3,4,5,6-Dibenzo-9-thiafluorene	92	17
3	2-(1′-Naphthylmercapto)-1-tetralone	92	1,2-Dihydro-3,4,7,8-dibenzo-9-thiafluorene	96	1,2,5,6-Dibenzo-9-thiafluorene	86	17

which was employed in the condensation of thiophenol[47] and naphthalene-1,5-dithiol.[39] Cyclodehydration of the 2-arylmercaptocycloalkanones was generally effected by the action of the following reagents: (1) P_2O_5 at 160–180°, (2) P_2O_5–H_3PO_4 mixture at 175–190° in vacuum or at atmospheric pressure, (3) P_2O_5 in boiling benzene or chlorobenzene. The hydroaromatic condensed thiophenes obtained were dehydrogenated by several agents, although treatment with selenium at 300–350° gave best results.[45]

TABLE 4.—CONDENSED THIOPHENES FROM DIARYLS
(Method IV)

No.	Diaryls used	Condensed thiophenes obtained by thionation	% Yield	Ref
1	*p*-Terphenyl	Benzo-(1,2-*b*,4,5-*b'*)-dithionaphthene (18%) Benzo-(2,1-*b*,3,4-*b'*)-dithionaphthene (27%)	22 (Mixture)	11
2	*m*-Terphenyl	Benzo-(1,2-*b*, 5,4-*b'*)-dithionaphthene Benzo-(1,2-*b*, 3,4-*b'*)-dithionaphthene Benzo-(1,2-*b*, 4,5-*b'*)-dithionaphthene		14
3	2:2'-Dithionaphthenyl	Thieno-(3,2-*b*, 4,5-*b'*)-dithionaphthene		14
4	3:3'-Dithionaphthenyl	Compound (A), m.p. 190°, + thieno-(3,2-*b*, 4,5-*b'*)-dithionaphthene (in presence of $AlCl_3$) compound m.p. 200° (without $AlCl_3$)		14,46
5	2:3'-Dithionaphthenyl	Compound (A), m.p. 190°, + thieno-(3,2-*b*, 4,5-*b'*)-dithionaphthene		14,46
6	3-Phenylthionaphthene	Thionaphtheno-(3,2-*b*)-thionaphthene (in presence of $AlCl_3$)	7	19,48
		Thionaphtheno-(2,3-*b*)-thionaphthene (without $AlCl_3$)	20	18,48

Synthesis of condensed thiophenes from diaryls.[11,14] Among the different methods available for the synthesis of condensed thiophenes, the one step synthesis from diaryls by interaction with sulphur and anhydrous aluminium chloride is an attractive route which does not appear to have been much studied. The approach (Method IV) has now been studied in the case of 2 and 3-phenyl thionaphthenes; *meta*- and *para*-terphenyls, 2,2'-,3,3'-, and 2,3'-dithionaphthenyls and the results obtained are summarized in Table 4.



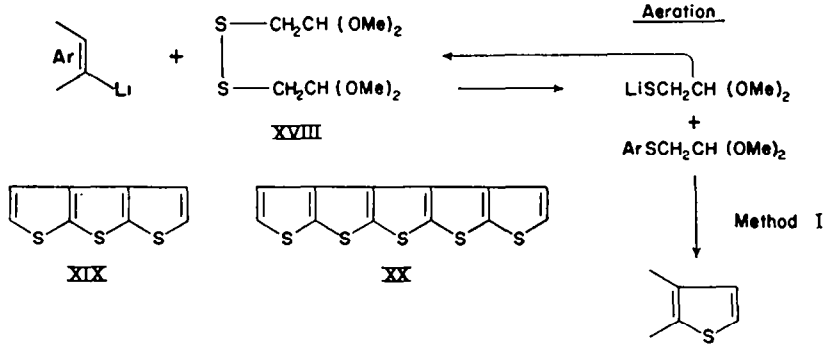
Method IV. Aluminium chloride used in the thionation effects partial isomerization of the diaryls. Several isomeric condensed thiophenes are, therefore, formed in the above synthesis and the structures of the condensed thiophenes so obtained have to be proved in each case. In the latter connection, aluminium chloride induced

isomerization of the diaryls has also to be studied. In spite of these limitations, this route is still attractive, since the condensed thiophenes which result are often otherwise difficultly accessible, and also because the mixture of the isomeric condensed thiophenes is easily separable. The method, however, suffers from low yield of the thionation products.

Very recently 3-phenylthionaphthene has been converted to thionaphtheno-(2:3-*b*)-thionaphthene by thionation with sulphur alone and it appears that aluminium chloride-induced isomerizations can thus be avoided.[48] In fact when this thionation was carried out in presence of aluminium chloride, the isomer thionaphtheno-(3:2-*b*)-thionaphthene was obtained, whereas 2-phenylthionaphthene when treated with sulphur and aluminium chloride did not yield the above condensed thiophene.[48]

Method IV is likely to prove of general interest and with this end in view synthesis of several diaryls containing benzene, thiophene, naphthalene and thionaphthene ring systems has been undertaken in this laboratory as discussed later (Method VII).

Synthesis of condensed thiophenes from aryllithium derivatives (Method V). A novel and general synthesis (Method V) of aryl ω-dimethoxyethyl sulphides dispenses with the need of starting with thiols (foul smelling!) required in the synthesis of condensed thiophenes by Method I discussed earlier.[21,49] The method may be outlined as follows:



Method V. The above method has led to the synthesis of the known condensed thiophenes such as thionaphthene, thieno-(2:3-*b*)-thiophene, naphtho-(1′:8′-*bc*)-thiapyran, 6:7-benzothionaphthene, and thieno-(2:3-*b*)-thionaphthene, in addition to the hitherto inaccessible condensed thiophenes: thieno-(3:4-*b*, 5:4-*b*′) dithiophene (XIX) and thieno-(3:4-*b*)-pyrene (XIIA, the thioster of the potent carcinogen 3:4-benzpyrene). Compounds prepared by the method are listed in Table 5. This synthesis opens a possible route to thiosters of polycenes, since the process of metalation and interaction with XVIII may be repeated on XIX, leading ultimately to the pentacene analogue XX. However, the bond angles of the sulphur atom linked in these compounds will be so much deviated from those in thiophene, that a *cis*-build up of thiophene rings beyond the tetra or pentacyclic stage may be very difficult if not impossible. A pentacene analogue containing five *cis*-fused thiophene rings (XX) could be built up with a Courtauld model[50] with adjustable bonds, but the molecule was highly strained. Attempts at the synthesis of a pentacene analogue have already

[48] T. S. Murthy and B. D. Tilak, Unpublished work.
[49] L. J. Pandya and B. D. Tilak, *J. Sci. Ind. Res., India* **18B**, 371 (1959).
[50] R. Robinson, *Disc. Faraday Soc.* **16**, 125 (1954).

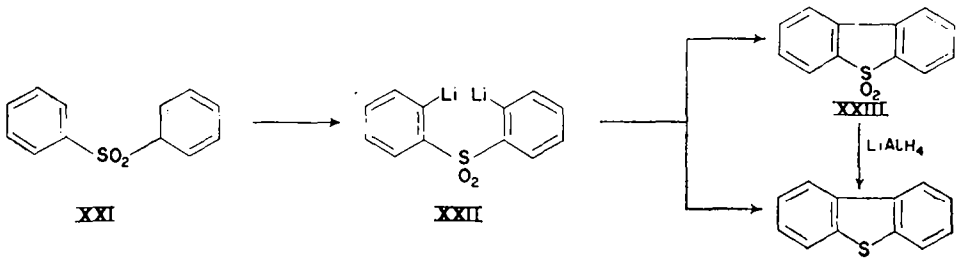
TABLE 5. CONDENSED THIOPHENES FROM ARYLLITHIUM DERIVATIVES

No.	Starting materials	Aryllithium derivative	Aryl ω-dimethoxyethyl sulphide (acetal)	% Yield from the starting material	Condensed thiophenes	% Yield from the acetal	Ref.
1	Bromobenzene	Phenyllithium	ω-Dimethoxyethyl phenyl sulphide	97	Thionaphthene	41	21,49
2	Thiophene	2-Thienyllithium	ω-Dimethoxyethyl 2-thienyl sulphide	42	Thieno-(2,3-*b*)-thiophene	11	21,49
3	α-Bromonaphthalene	α-Naphthyllithium	ω-Dimethoxyethyl α-naphthyl sulphide	45	A mixture of naphtho-(1′,8′-*bc*)-thiapyran and 6,7-benzothio-naphthene.	34	21,49
4	Thionaphthene	2-Thionaphthenyl-lithium	ω-Dimethoxyethyl 2-thio-naphthenyl sulphide	69	Thieno-(2,3-*b*)-thio-naphthene	36	21,49
5	2-Bromopyridine	2-Pyridyllithium	ω-Dimethoxyethyl 2-pyridyl sulphide	54	Did not cyclize	—	21,49
6	2,5-Di-iodothiophene	Thienyl-2,5-dilithium	2,5-Bis-ω-dimethoxyethyl-mercaptothiophene	58	Thieno-(2,3-*b*,5,4-*b*′) dithiophene	33	21,49
7	3-Bromopyrene	3-Pyrenyllithium	ω-Dimethoxyethyl 3-pyrenyl sulphide		Thieno-(3,4-*b*)-pyrene	low	21,49

been undertaken, as also the synthesis of a dithiophene analogue of 3:4,9:10-dibenzpyrene (the suspected carcinogenic factor in tobacco tar)[51] starting from 3,10-dibromopyrene.

Synthesis of condensed thiophenes from diaryl sulphones. A few condensed thiophenes have been synthesized by the cyclization of diaryl sulphides by the action of arylsodium and/or aryllithium[52] derivatives, and by the action of sodium amide on diaryl sulphoxides.[53] In view of the formation of diphenyl sulphone-2,2′-dilithium (XXII) from diphenyl sulphone (XXI)[54] and the synthesis of 2,2′- and 3,3′-dithionaphthenyls from 2- and 3-bromothionaphthenes by the action of cupric chloride on the corresponding Grignard reagents,[40] the possibility of cyclization of XXII by interaction with cupric chloride was investigated. It is of interest to record that a little of dibenzothiophene was formed along with the expected sulphone XXIII (yield 70%). The latter was then readily converted to dibenzothiophene in good yield by reduction with lithium aluminium hydride.[55] This synthesis (Method VI) may also prove to be of general interest for the preparation of other condensed thiophenes from diaryl sulphones as well as for the synthesis of dialkyls, diaryls, and diarylenes.

Experiments in this direction have been already undertaken.



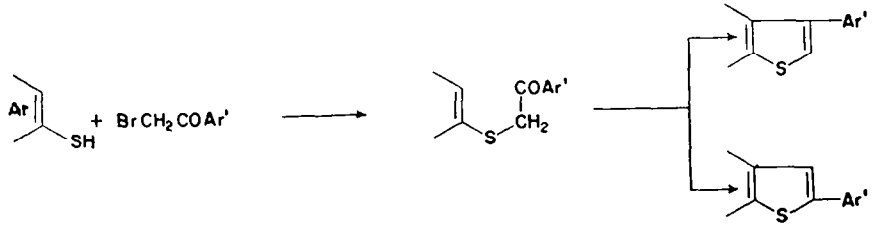
XXI XXII XXIII

Method VI: *Synthesis of alkyl and aryl derivatives of condensed thiophenes* (Method VII). Synthesis of 3-alkyl and 2,3-dialkyl thionaphthenes by cyclodehydration of aryl 2-ketoalkyl sulphides (Ar—S—CHR—CO—R′) has been reported by Werner.[56] Banfield *et al.*[57] have suggested that cyclodehydration of sulphides represented by the general formula Ar—S—CH_2—CO—R leads to 3-alkylthionaphthenes, where R is an alkyl group, and to 2-arylthionaphthenes where R is an aryl group. A re-investigation of Banfield's work has revealed that both 2-aryl and 3-aryl thionaphthenes were formed when aryl aroylmethyl sulphides were treated with polyphosphoric acid at 170–180°.[58] The structure of 3-arylthionaphthenes was proved by two unambiguous synthesis involving the Grignard reaction: (1) starting from 3-halo-(iodo or bromo) thionaphthene (and related compounds) and cyclohexanones[58]

[51] B. D. Tilak, M. K. Unni and K. Venkataraman, *Tetrahedron* **3**, 62 (1958).
[52] *a* A. Luttringhous, G. Wagner, E. Sucker and G. Borth, *Liebigs Ann.* **557**, 54 (1945); *b* G. Wittig and E. Benz, *Chem. Ber.* **91**, 873 (1958).
[53] *a* J. H. Freeman and C. E. Scott, *J. Amer. Chem. Soc.* **77**, 3384 (1955); *b* H. Gilman and D. R. Swayampati, *J. Org. Chem.* **21**, 1273 (1956); *c* R. Wilputte, *Bull. Soc. Chem. Belg.* **65**, 674–698 (1956); *Chem. Abstr.* **51**, 6589^c (1957).
[54] *a* W. E. Truce and M. F. Amos, *J. Amer. Chem. Soc.* **73**, 3013 (1951); *b* E. A. Lehto and D. A. Shirley, *J. Org. Chem.* **22**, 989 (1957).
[55] V. S. Palkar and B. D. Tilak, Unpublished work.
[56] E. G. G. Werner, *Rec. Trav. Chim.* **68**, 509 (1949).
[57] J. E. Banfield, W. Davies, N. W. Gamble and S. Middleton, *J. Chem. Soc.* 4791 (1956).
[58] D. S. Rao and B. D. Tilak, *J. Sci. Ind. Res., India* **18B**, 77 (1959).

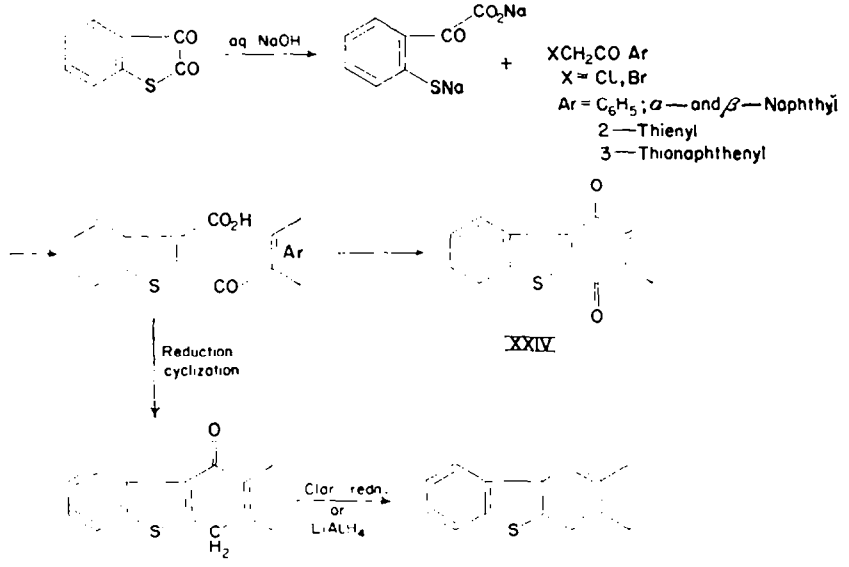
and (2) starting from thioindoxyl (and related compounds) and arylhalides (bromo or iodo).[48]

The 2-aryl and 3-aryl-thionaphthenes and related compounds which were synthesized by cyclodehydration of compounds of the type Ar—S—CH_2—COAr′ are listed in Table 6. The general method of synthesis (Method VII) may be represented as follows:



Method VII: A reaction mechanism to account for the formation of the two isomeric arylthionaphthenes in the above method has been suggested.[58] The relation between the yield of the two isomers and chemical structure of the intermediate sulphides is under investigation. Another point of interest in this study is the possible use of the arylthionaphthenes in the synthesis of condensed thiophenes by the Method IV discussed above.

Synthesis of condensed thiophenes from thiophanthrenequinones and related compounds. Thiophanthrenequinones and related benzo-derivatives were prepared from thioisatin as follows:



Method VIII. The above method was first suggested by Mayer[81] and was used subsequently by the author for the synthesis of several thiophanthrenequinones of the type XXIV,[3,4,10,15] which were required in the synthesis of *meso*-dimethyl derivatives. The latter compounds were required in the study of chemical carcinogenesis discussed earlier in the paper.

TABLE 6. SYNTHESIS OF ALKYL OR ARYLTHIONAPHTHENES FROM α-ARYLMERCAPTOKETONES

No.	α-Arylmercaptoketones	% Yield from thiol	Alkyl or arylthionaphthenes	% Yield from α-aryl mercapto-ketone	Ref.
1	Phenyl phenacyl sulphide	95	3-Phenylthionaphthene,	15	58
			2-Phenylthionaphthene	44	57,59
2	*p*-Tolyl phenacyl sulphide	86	5-Methyl-2-phenylthionaphthene,	36	57
			5-Methyl-3-phenylthionaphthene.	25	58
3	α-Phenylmercaptopropiophenone	82	2-Methyl-3-phenylthionaphthene, b.p. 110–115° (bath temp)/0·01 mm.	82	48
4	*p*-Methoxyphenacyl phenyl sulphide	84	3-(*p*-Methoxyphenyl)-thionaphthene, b.p. 130–35° (bath temp)/0·01 mm.	17	48
			2-(*p*-Methoxyphenyl)-thionaphthene	34	57
5	β-Naphthyl phenacyl sulphide	66	3-Phenyl-4:5-benzothionaphthene,	54	48,59
			2-Phenyl-4:5-benzothionaphthene.	10	
6	α-Naphthacyl phenyl sulphide	80	3-(α-Naphthyl)-thionaphthene, m.p. 92°	36	48
			2-(β-Naphthyl)-thionaphthene, m.p. 212°	4	60
7	β-Naphthacyl phenyl sulphide	88	3-(β-Naphthyl)-thionaphthene, m.p. 60°	38	48
			2-(β-Naphthyl)-thionaphthene, m.p. 212°	13	
8	2-Thienoacetyl phenyl sulphide	77	3-(2′-Thienyl)-thionaphthene, b.p. 160–65° (bath temp)/2·5 mm.	32	48
			2-(2′-Thienyl)-thionaphthene, m.p. 156°	16	
9	2-Thionaphthacyl phenyl sulphide	18	2,3′-Dithionaphthenyl, m.p. 76°	—	40
10	3-Thionaphthacyl phenyl sulphide	46	3,3′-Dithionaphthenyl, m.p. 85°	16	40
11	2-Thionaphthenyl phenacyl sulphide	72	3-Phenyl-thionaphtheno-(2,3-*b*)-thiophene, m.p. 78°	90	48

Removal of the quinone group in the above thiophanthrenequinones by reduction appeared to be an attractive route for the synthesis of several condensed thiophenes which are of interest in the above study of chemical carcinogenesis. The reduction step, however, proved difficult, and with the exception of 2:3-benzo-4:9-thiophanthrenequinone which was reduced by zinc and ammonia in poor yield (cf. Mayer),[61] the other quinones were not amenable to reduction by means of milder methods such as, treatment with zinc and alkali, lithium aluminium hydride, two step reduction by conversion to anthrone and subsequent reduction by zinc and alkali. When a more drastic method of reduction such as zinc dust distillation was employed, the sulphur atom was removed (e.g. formation of 3-phenylphenanthrene from 2:3,7:8-dibenzo-4,9-thiophanthrenequinone[3]) and under milder conditions such as Clar reduction, the intermediate anthrones were obtained.[3,4] Recently two condensed thiophenes have been prepared in low yield by the reaction sequence outlined above (Method VIII).

By employing the above procedure, compounds VIA and VIIIA (see Chart I), the thiosters of the carcinogens 1:2,5:6-dibenzanthracene and 1:2,7:8-dibenzanthracene, have been prepared in low yield.[13] In view of the facile synthesis of anthrones [either through the diarylmethane-*o*-carboxylic acids (as outlined above) or by reduction of quinones], the above method of removal of the quinone groups may prove of general interest. Thus anthraquinone and 2-methylanthraquinone have been reduced to anthracene and 2-methylanthracene through the corresponding anthrones, either by Clar reduction or by the action of lithium aluminium hydride.

Although the above synthetical methods for condensed thiophenes were initially developed in connection with the synthesis of thiosters of carcinogenic hydrocarbons, the work is also interesting in the study of the following:

(1) Precise nature and extent of isosterism between thiophene and benzene in their polycyclic derivatives,

(2) fine structure of fused thiophene ring systems,

(3) general chemistry of condensed thiophenes and

(4) nature of sulphur containing compounds in the higher boiling fractions of petroleum. Indeed, on account of the latter interest, major portion of the work on condensed thiophenes in progress over the last three years, has been financed, out of a generous grant from the Petroleum Research fund of the American Chemical Society. The condensed thiophenes are also being studied under the American Petroleum Institute Research Project 48, which deals with the synthesis, properties and identification of sulphur compounds in petroleum.

Acknowledgements—I am indebted to Sir Robert Robinson at whose suggestion the work was initiated in 1944 at Oxford. I am also grateful to my research colleagues whose work is referred to herein. This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgement is hereby made to the donors of the said fund.

[59] O. Dann and Kokorudz, *Chem. Ber.* **91**, 172 (1958).
[60] R. Schuetz and L. Ciporin, *J. Org. Chem.* **23**, 206 (1958).
[61] F. Mayer, A. Mombour, W. Lassman, W. Werner, W. Laudmann P. and E. Schneider, *Liebigs Ann.* **485**, 259 (1931).