A NEW SYNTHESIS OF THIOPHENES AND THIAPYRANS[1]

Part I. A New Synthesis of Thionaphthene, Its Scope and Limitations

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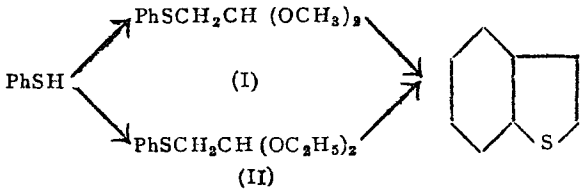
With the discovery of penicillin, α- and β-biotins, increased attention is being devoted in recent years to the synthesis of heterocyclic compounds where sulphur forms a part of the ring system. The close similarity in the physical and chemical properties of benzene and thiophene and their analogous derivatives, led Erlenmeyer to suggest the equivalence, "isosterism", of a divalent sulphur atom to the group,—CH = CH —("pseudo-atom"), such compounds being termed "isosters".[2] A number of sulphur isosters of physiologically active compounds have been reported, the comparative activity of the two series of compounds have been studied, and in many cases it has been found that the sulphur isosters showed similar physiological action.

In connection with the preparation of sulphur isosters of carcinogenic hydrocarbons,[1] the syntheses of thionaphthene and its higher polycyclic derivatives were studied. The methods available for the synthesis of thionaphthene are: (1) condensation of *o*-mercaptobenzaldehyde with chloroacetic acid in alkaline solution followed by the decarboxylation of the resulting thionaphthene-2-carboxylic acid,[3] (2) cyclization of *o*-mercaptocinnamic acid,[4] (3) cyclization of *o*-mercaptostyrene,[5] (4) reaction of styrene with hydrogen sulphide at 625° in presence of ferrous sulphide-aluminium oxide catalysts,[6] (5) reaction of ethylbenzene with hydrogen sulphide at 575° using chromia on alumina catalyst[7] and (6) the reduction of thioindoxyl with zinc and acetic acid.[8] The last method has also been widely used in the syntheses of substituted thionaphthenes and higher polycyclic derivatives of thionaphthene, but it suffers from two main disadvantages: the instability of thioindoxyls due to air oxidation and the low yields in their conversion to thionaphthenes.[8, 9]

Attempts have been made to synthesise thionaphthenes by the ring-closure of α-phenylmercapto ketones and aldehydes in analogy with the

syntheses of benzofurans. Thus Delisle[10] made unsuccessful attempts to cyclize phenyl acetonyl sulphide. Autenrieth[11] likewise failed to cyclize phenyl ω-diethoxyethyl sulphide (II) by treatment with acidic reagents. The synthesis of 6-hydroxy-3-phenylthionaphthene by cyclization of 3-hydroxyphenyl phenacyl sulphide with sulphuric acid, is the only example of cyclization in the thionaphthene series.[12] The failure to synthesise thionaphthenes has been attributed by Bradsher[13] to the instability of the phenyl sulphydryl ketones and aldehydes, as also to the low order of *ortho* activation by the thioether group. Werner[14] has however recently synthesised a series of thionaphthenes with substitutents in two and/or three positions by cyclization of α-arylmercaptoketones by treatment with a mixture of zinc chloride and phosphorus pentoxide.

Ring-closure of phenyl ω-dimethoxyethyl sulphide (I) by treatment with acidic dehydrating agents, such as sulphuric acid of varying strengths; sulphuric acid in acetic acid or glycerine; phosphorus oxychloride; anhydrous aluminium chloride, stannic chloride and phosphorus oxychloride in dry benzene; phosphorus pentoxide and phosphoric acid sp.gr. 1·75, was studied. It is found that cyclization of (I) and (II) with a mixture of phosphorus pentoxide and phosphoric acid gives thionaphthene in an optimum yield of 37 and 32 per cent. respectively.



The synthesis of thionaphthene has been extended to mono-substituted thionaphthenes containing substituents such as, methyl, chloro, hydroxy, alkoxy, etc. Starting from naphthalene mono and dithiols, polycyclic compounds containing naphthalene and thiophene or thiapyran ring systems have also been prepared. Phenanthrene monothiols led to more complex sulphur-containing polycyclic compounds. The work will be reported in subsequent communications.

The new synthesis, in general, consists in the reaction of aryl thiols Ar $(SH)_n$ with bromoacetaldehyde dimethyl acetal followed by the cyclization of aryl ω-dimethoxyethyl sulphides (S-arylthioglycolicaldehyde dimethyl acetals) Ar $[SCH_2CH(OMe)_2]_n$ to give sulphur-containing heterocyclic compounds. The only requisites appear to be aryl thiols with free *o*- or *peri* positions to the thiol groups to enable the cyclization of the thioglycolic aldehyde dimethyl acetal side chain $[SCH_2CH(OMe)_2]_n$.

The scope of the synthesis is indicated by the variety of compounds which have so far been synthesised by this method. Unlike the syntheses of higher polycyclic thiophene derivatives starting from a performed thiophene ring system, in the present synthesis a five- or a six-membered sulphur-containing ring is built up on an aryl residue. The scope of the synthesis in the preparation of monosubstituted thionaphthenes appears to be limited to 5-, 6- and 7-substituted derivatives. *o*- and *p*-Substituted aryl thiols lead to 7- and 5-substituted thionaphthenes respectively. In the case of *m*-substituted aryl thiols the cyclization of the intermediate thioglycolic-aldehyde dimethyl acetals may yield 4- or 6-substituted thionaphthenes depending on the direction of cyclization. The formation of 4-substituted thionaphthenes is, however, probably minimised or precluded because of steric hindrance. Mono-substituted thionaphthenes prepared in the present work from *m*-substituted aryl thiols have, therefore, been constituted as 6-substituted derivatives, although the formation of the 4-substituted isomers in low yields cannot be ruled out. It may be noted that among the monosubstituted thionaphthenes, with the exception of 2- and 3-substituted thionaphthenes, only a few thionaphthenes with substituents in the benzene half of the molecule are known. These are now readily synthesised by the new method.

Another limitation of the synthesis at present appears to be the drastic treatment with phosphorus pentoxide and phosphoric acid involved in the cyclization of the intermediate sulphides, which may preclude its application to compounds which are unstable under these conditions. Further experiments to effect cyclization of the intermediate sulphides such as (I) under milder conditions have been undertaken.

Experimental

(Microanalyses are by Drs. Weiler and Strauss, Oxford, Melting points are uncorrected.)

General method for the preparation and characterization of aryl ω-dimethoxyethyl sulphides

An absolute alcoholic solution of the aryl thiol (1 mol.) was added to a solution of sodium ethoxide (1 mol.) in absolute alcohol followed by the addition of sodium iodide (about 0·1 mol.) and bromoacetaldehyde dimethyl acetal[15] (1 mol.). The mixture was heated under reflux for 2–6 hours and the excess of alcohol was removed by distillation. The residue was diluted with water and the crude sulphide was isolated by means of ether and purified by distillation under reduced pressure. The sulphide was characterised by preparation of the 2:4-dinitrophenylhydrazone of the parent *S*-aryl-thioglycolic-aldehyde by addition to an alcoholic solution of 2:4-dinitro-

phenylhydrazine containing a few drops of concentrated sulphuric acid and warming the mixture.

General method for the ring-closure of liquid sulphides

The sulphides (5 g.) were added gradually through a separating funnel to a mixture of phosphorus pentoxide (20–25 g.) and syrupy phosphoric acid, sp.gr. 1·75 (12–15 c.c.), kept in a distilling flask and previously heated under reduced pressure to a temperature near the boiling point of the sulphides. It was necessary to add the sulphides below the surface of the phosphorus pentoxide-phosphoric acid mixture to get an optimum yield of the cyclized product. After each addition a vigorous reaction set in with simultaneous distillation of the crude cyclized product usually in the form of a colourless liquid. The distillate was treated with excess of saturated alcoholic solution of picric acid, the picrate obtained was decomposed with alkali and the cyclized product was isolated by means of ether or by steam distillation. An alternative method for the decomposition of the picrate was to pass a benzene solution of the picrate through a column of activated alumina.

Phenyl ω-dimethoxyethyl sulphide (I)

A mixture of thiophenol[16] (35·1 g.), sodium (7·4 g.), sodium iodide (4·8 g.), bromoacetaldehyde dimethyl acetal (54·1 g.) and absolute alcohol (170 c.c.) was boiled for 3 hours. The crude sulphide (51·4 g.) gave a colourless liquid after distillation, b.p. 130–32°/6 mm. (47·8 g.; yield 76%). It was further purified by redistillation and finally collected at b.p. 170–75° (bath temp.)/6 mm. (Found: C, 60·1; H, 7·0; S, 16·0. $C_{10}H_{14}O_2S$ requires C, 60·6; H, 7·1; S, 16·2%). 2:4-*Dinitrophenylhydrazone* after crystallization from alcohol gave lustrous yellow-orange needles, m.p. 102·5–103·5° (Found: N, 17·3. $C_{14}H_{12}N_4O_4S$ requires N, 16·9%).

Ring-closure of the sulphide (I)

The different attempts to cyclize (I) are summarised in Table I. Only those experiments where thionaphthene was obtained as shown by the formation of the picrate, m.p. 150°, have been included in the table. The experiment (No. 8) where an optimum yield of thionaphthene (37%) was obtained is described below.

The sulphide (15 g.) was added to a mixture of phosphorus pentoxide (60 g.) and phosphoric acid (36 c.c.) at 160°/5 mm. The colourless distillate (7·25 g.) was treated with a saturated alcoholic solution of picric acid (45 g.). The picrate was decomposed with 5% sodium hydroxide solution and thionaphthene was isolated by means of ether. Removal of ether gave thionaphthene in the form of colourless flakes, m.p. 30–32° (3·94 g.; yield 37%).

The picrate after recrystallization from alcohol gave long yellow needles, m.p. 151° (Found: S, 9·0. Calc, for $C_{14}H_9N_3O_7S$: S, 8·8%).

Phenyl ω-diethoxyethyl sulphide (II)

Sodium (2·3 g.), thiophenol (10·3 c.c.), sodium iodide (1·5 g.), chloro acetaldehyde diethyl acetal (15·3 g.) and absolute alcohol (50 c.c.) were boiled for 2 hours. The sulphide gave a colourless liquid after distillation b.p. 120–30°/2 mm. (Autenrieth,[10] gives b.p. 273°) and gave a 2: 4-dinitrophenylhydrazone identical with the hydroazone prepared from (I).

Ring-closure of the sulphide (II)

The sulphide (2·5 g.) when treated with a mixture of phosphorus pentoxide (10 g.) and phosphoric acid (6 c.c.) at 160°/2 mm., gave thionaphthene (0·48 g., yield 32%) which was isolated through the picrate.

TABLE I

Experiment No.	Amount of (I) g.	P_2O_5 g.	H_3PO_4 sp.gr. 1·75, c.c.	Yield of crude thionaphthene g.	Yield of pure thionaphthene isolated through picrate		Procedure
					g.	%	
1	2·5	10	6	..	0·1	..	(I) Added to P_2O_5–H_3PO_4 mixture at 140-50°. Thionaphthene isolated by steam distillation
2	2·5	20	12	..	0·09	..	As above. Mixture heated for 15 minutes
3	2·5	5	..	0·14	..	..	Mixture of (I) and P_2O_5 heated in vacuum. Vigorous reaction takes place at 110° (bath temp.), and a pale yellow oil, b.p. 60°/5 mm., distills over
4	2·5	7·5	..	0·14	..	..	Mixture of (I) and P_2O_5 distilled at atm. pressure
5	3	7·5	..	0·7	..	..	(I) Added dropwise to P_2O_5 kept at 140-50°/5 mm. Colourless liquid (0·7 g.) distills over
6	2	5	3	0·63	0·135	10	(I) Added to P_2O_5–H_3PO_4 mixture at 140-50°/10 mm. during 16 min., mixture heated for 15 min. Crude product was purified through picrate
7	3·2	13·2	8	0·805	0·28	13	(I) Added to P_2O_5–H_3PO_4 mixtr. during 5 min. at 150–60/4 mm. mixture then heated to 200°. The crude product was purified through picrate
8	15	60	36	7·25 (72·5%)	3·94	37	(I) Added below the surface of P_2O_5–H_3PO_4

SUMMARY

Cyclization of phenyl ω-dimethoxyethyl sulphide (I) under different conditions was studied and an optimum yield of 37% of thionaphthene was obtained by treatment with a mixture of phosphorus pentoxide and phosphoric acid under closely defined conditions. Phenyl ω-diethoxyethyl sulphide (II) also gave thionaphthene in 32% yield under similar conditions.

The new synthesis of thionaphthene, which has been extended to substituted thionaphthenes and to other thiophenes and thiapyrans reported in subsequent communications consists in the cyclization of aryl ω-dimethoxyethyl sulphides Ar $[SCH_2CH(OMe)_2]_n$. The scope and limitations of the new synthesis are discussed.

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