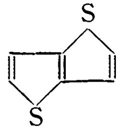
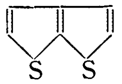
62. *Some Substitution Products of Thiopheno-2′ : 3′-3 : 2-thiophen.*

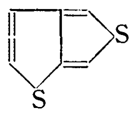
By Frederick Challenger and Geoffrey M. Gibson.

The solid isomer of thiophthen gives a *monochloromercuri*-derivative, convertible by acetyl and propionyl chlorides into thiophthienyl methyl and ethyl ketones identical with those obtained from thiophthen and the acid chlorides with stannic chloride as catalyst. These ketones are oxidised to a *thiophthencarboxylic acid* (characterised as the *methyl* and the p-*nitrobenzyl* ester and as the *anilide*) identical with that obtained by heating thiophthen with ethylmagnesium bromide and treating the product with carbon dioxide. With an excess of the Grignard reagent, a thiophthendicarboxylic acid is obtained. Thiophen gives thiophen-2-carboxylic acid with ethylmagnesium bromide.

It was shown by Challenger and Harrison (*J. Inst. Pet. Tech.*, 1935, **21**, 135) that the distillate obtained by passing acetylene over boiling sulphur yields a fraction, b. p. 90—120°/15 mm., which gives a picrate, m. p. 139—141°. On decomposition with sodium carbonate an oil is obtained consisting of two isomeric thiophthens. On freezing, it deposits a solid which when purified melts at 54° and by *X*-ray analysis and its zero dipole moment was identified as thiopheno-2′ : 3′-3 : 2-thiophen (I). The liquid portion of the oil when purified through the styphnate is probably identical with the liquid thiophthen obtained by Biedermann and Jacobson (*Ber.*, 1886, **19**, 2444) by heating citric acid with phosphorus trisulphide. This is probably thiopheno-2′ : 3′-2 : 3-thiophen (II), although the structure (III) is not excluded.


(I.)


(II.)


(III.)

For convenience, unless otherwise stated, the terms " thiophthen " and " thiophthienyl " as used in this communication will refer solely to the solid isomer (I).

Three isomeric selenophthens have been prepared by Umezawa *et al.* (*Bull. Chem. Soc. Japan*, 1939, **14**, 310, 318, 363).

Thiophthen with or without sodium acetate is readily converted by mercuric chloride into a mixture of mercury derivatives, from which a *monochloromercuri*-compound may be isolated. This with propionyl chloride gives *thiophthienyl ethyl ketone* identical with, and giving the same 2 : 4-*dinitrophenylhydrazone* as a specimen prepared from thiophthen, propionyl chloride and stannic chloride.

Acetyl chloride also eliminates the chloromercuri-group, giving thiophthienyl methyl ketone (Challenger and Harrison, *loc. cit.*, p. 152). This was converted into the *phenylhydrazone* and the 2 : 4-dinitrophenylhydrazone, which were found to be identical with authentic specimens. There is no evidence in favour of an abnormal course of the replacement of HgCl by R·CO.

Thiophthienyl methyl and ethyl ketones on oxidation with sodium hydroxide and iodine and with potassium ferricyanide respectively give the same *thiophthencarboxylic acid*. The former is an excellent agent for this purpose; the latter is somewhat inconvenient owing to the bulk of liquid employed. Potassium permanganate tends to cause complete oxidation, and potassium hypobromite was shown by Challenger and Harrison (*loc. cit.*, p. 140) to produce brominated carboxylic acids when applied to the oxidation of the methyl ketone of the liquid isomer of thiophthen.

The carboxylic acid obtained by the interaction of thiophthen and ethylmagnesium bromide (compare Challenger and Miller, J., 1938, 894) and treatment of the product with carbon dioxide is identical with the acid obtained by oxidation of the ketones. This was confirmed by preparation of the *methyl* and the p-*nitrobenzyl* ester from both specimens.

The replacement of HgCl by R·CO being assumed to proceed normally, it follows that the direct introduction of HgCl, CH_3·CO, C_2H_5·CO, and MgBr into the thiophthen nucleus occurs in the same position.

The case of thionaphthen is different. Introduction of Br, NO_2, CH_3·CO, and AcO·Hg, takes place in position 2, whereas substitution by Na or by MgBr occurs in position 1 (see Challenger and Miller, J., 1939, 1006, for references). The exclusive *o*-substitution observed by these authors (J., 1938, 894) when R·MgBr reacts with anisole and phenetole has an interesting analogy in the conversion of *p*-bromoanisole into 5-bromo-2-methoxyphenyl-lithium by *p*-anisyl-lithium. This was converted by carbon dioxide into 5-bromo-2-methoxybenzoic acid (Gilman and Jacoby, *J. Org. Chem.*, 1938, **3**, 108). Further evidence of the reactivity of the *o*-position in anisole towards organo-metallic derivatives is furnished by Wittig, Pockels, and Dröge (*Ber.*, 1938, **71**, 1903), who showed that, when phenyl-lithium reacts with anisole, *p*-bromoanisole, or resorcinol dimethyl ether, lithium enters the *o*-position to the methoxy-group (see also Müller and Töpel, *Ber.*, 1939, **72**, 276).

The interaction of ethylmagnesium bromide with thiophen gave thiophen-2-carboxylic acid. Careful fractionation failed to detect any of the 3-isomer. Schorigin (*Ber.*, 1910, **43**, 1938) also obtained thiophen-2-carboxylic acid by heating diethylmercury and thiophen with sodium and treating the product with carbon dioxide.

EXPERIMENTAL.

Thiophthienyl Ethyl Ketone.—A solution of thiophthen (4 g.) and propionyl chloride (5 g.) in carbon disulphide (50 c.c.) was slowly added to stannic chloride (25 g.) in 50 c.c. of the same solvent (calcium chloride tube). During 4 hours a dark tar gradually separated. The whole was then poured into ice-water and warmed till the tar was replaced by a greenish-blue solid. The red carbon disulphide layer was evaporated, leaving an oil which quickly solidified. This together with the solid was distilled in steam, giving a white volatile *ketone*, m. p. 90—94°, and 92—92·5° after two recrystallisations from aqueous alcohol; yield, 4·9 g. (88%). In a second experiment lasting only 2 hours the yield was 81% (Found : C, 55·0; H, 4·2; S, 32·8. $C_9H_8OS_2$ requires C, 55·1; H, 4·1; S, 32·65%).

The 2 : 4-*dinitrophenylhydrazone* was prepared in alcohol containing a little hydrochloric acid. The red solid was washed with alcohol, boiled with ethyl acetate, and recrystallised from alcohol–chloroform; m. p. 251—252° (Found : N, 14·9; S, 17·05. $C_{15}H_{12}O_4N_4S_2$ requires N, 14·9; S. 17·1%).

Mercuration of Thiophthen.—Thiophthen (5 g.), sodium acetate (5 g.), mercuric chloride (10 g.), and 70% aqueous alcohol (75 c.c.) were shaken overnight, the mixture diluted with water (75 c.c.), and the solid separated. This was washed with water and ether and boiled for 3 hours with acetone–benzene (250 c.c.). The process was repeated several times. The extracts deposited white crystals of *monochloromercurithiophthen* in about 20% yield. The same product was formed, but more slowly, when sodium acetate was omitted (Found, for a specimen thus obtained : Hg, 53·4. $C_6H_3ClS_2Hg$ requires Hg, 53·5%).

The portion insoluble in acetone–benzene or in toluene consisted of a mixture of the mono- and the di-chloromercuri-derivative and was not purified.

Propionyl Chloride and Chloromercurithiophthen.—A thin paste of the mercury compound (1·15 g.) and propionyl chloride was left overnight in a closed flask; a vivid blue colour slowly developed. The mixture was poured on ice, neutralised with sodium hydroxide, and distilled in steam. Extraction of the distillate with benzene yielded a red solid, which was extracted with light petroleum and recrystallised from alcohol (charcoal). The colourless needles obtained had m. p. 91·5—92°, and 92—92·5° when mixed with authentic thiophthienyl ethyl ketone (m. p. 92—92·5°). Neither the alcoholic mother-liquors nor the light petroleum extract contained any thiophthen, the picrate test being negative (Found : C, 54·8; H, 4·2; S, 32·6. Calc. : C, 55·1; H, 4·1; S, 32·65%). The 2 : 4-dinitrophenylhydrazone melted at 251—252° alone and when mixed with an authentic specimen of the same m. p.

Acetyl Chloride and Chloromercurithiophthen.—The mercury compound (2·27 g.) was made into a paste with acetyl chloride; a purple colour gradually developed. After 30 minutes, the mixture was poured on ice. The greenish precipitate was extracted with alcohol, which removed a crude ketone. This after distillation in steam and recrystallisation from alcohol melted at 124·5—125° alone and in admixture with authentic thiophthienyl methyl ketone, m. p. 125° (Challenger and Harrison, *loc. cit.*, p. 152). The mother-liquors on distillation yielded a little thiophthen, identified as picrate, m. p. 145° (Challenger and Harrison, *loc. cit.*, p. 139)—see below. The dinitrophenylhydrazone of the ketone had m. p. and mixed m. p. 272° with an authentic specimen of the same m. p. (C. and H., *loc. cit.*, p. 139, give m. p. 267°, but this figure is low). This derivative is not easily purified when prepared in sulphuric acid solution. A much cleaner product is obtained by using aqueous 2 : 4-dinitrophenylhydrazine hydrochloride and recrystallising the substance from ethyl acetate. The *phenylhydrazone* had m. p. 163·5—164°, and 164° in admixture with an authentic specimen, m. p. 165·5—166°, prepared in 50% acetic acid and recrystallised three times from alcohol (Found : N, 10·65; S, 23·0. $C_{14}H_{12}N_2S_2$ requires N, 10·3; S, 23·55%).

The formation of thiophthen during the replacement of the chloromercuri-group by acetyl was probably due to the action of hydrochloric acid (produced from the excess of acetyl chloride on pouring into water) on the mercurichloride. When the reaction was carried out as before, and the mixture poured into excess of ice and 2N-sodium hydroxide, the formation of thiophthen was greatly diminished but not entirely suppressed. When hydrogen chloride was passed into a benzene suspension of chloromercurithiophthen for some hours, thiophthen and inorganic mercury were easily recognised. The small amount of thiophthen formed in presence of alkali may therefore have arisen from traces of hydrogen chloride present in the acetyl chloride or formed in a side reaction. No thiophthen was produced in the analogous experiment with propionyl chloride (see above).

Thiophthencarboxylic Acid (*K*).—(1) A solution of iodine (13·82 g.; 3·3 mols.) and potassium iodide (25 g.) in water (250 c.c.) was added drop by drop during 7 hours to a well-stirred suspension of thiophthienyl methyl ketone (3 g.) in approximately N-sodium hydroxide (150 c.c.). The mixture was shaken overnight, the iodoform and any unchanged ketone then extracted with ether, the aqueous solution acidified, and the liberated iodine reduced with sulphur dioxide. Extraction with ether yielded a pale yellow solid (2·9 g.; 97%), which crystallised from chloroform in colourless needles of constant m. p. 220—220·5° (without blackening) (Found : C, 45·2; H, 2·4; S, 34·5. $C_7H_4O_2S_2$ requires C, 45·65; H, 2·2; S, 34·8%). When the *acid* was heated with soda-lime, thiophthen was evolved; it was characterised as the picrate, m. p. 145° (C. and H., *loc. cit.*, p. 139). When the period of interaction of the ketone and the hypoiodite was reduced to 1½ hours and 4 hours, the yields of acid were 30% and 46% respectively. In the first experiment only 3 mols. of iodine were employed. Oxidation of the ketone with alkaline potassium ferricyanide gave a crude acid, m. p. 217—218°, which could not be purified by recrystallisation from water. The yield was 15%.

(2) A mixture of potassium ferricyanide (100 g.), potassium hydroxide (30 g.), water (250 c.c.), and thiophthienyl ethyl ketone (3 g.) was heated at 100° for 5 hours and left overnight. Unchanged ketone and potassium ferrocyanide were then separated, and the liquid acidified and extracted with ether, yielding a yellow solid (1·4 g.), m. p. 215—218° (decomp.), and 220—221° (decomp.) after four crystallisations from water (Found : C, 45·6; H, 2·5%).

The methyl ester was prepared from the acid (0·5 g.) and ethereal diazomethane from nitrosomethylurethane (1 c.c.) and 25% methyl-alcoholic potassium hydroxide (1·4 c.c.). The solution was shaken with dilute aqueous sodium carbonate (0·08 g. of acid recovered), washed, dried, and evaporated, giving a solid (0·51 g.), which crystallised from alcohol in colourless needles, m. p. 96·5—97° (Found : C, 48·4; H, 3·0; S, 32·2. $C_8H_6O_2S_2$ requires C, 48·5; H, 3·0; S, 32·4%). The same ester was obtained by means of methyl-alcoholic hydrogen chloride, but could not readily be purified and, moreover, was accompanied by a black solid which was probably a polymer.

The p-*nitrobenzyl* ester was obtained by exactly neutralising the acid (0·5 g.) with alcoholic potassium hydroxide (thymolphthalein) and heating the concentrated solution for 2 hours with *p*-nitrobenzyl bromide (0·57 g.; 0·97 mol.) and alcohol (10 c.c.). Recrystallised from acetone, the ester (0·45 g.) had m. p. 151·5—152° (Found : C, 51·9; H, 2·8; N, 4·6; S, 20·3. $C_{14}H_9O_4NS_2$ requires C, 52·7; H, 2·8; N, 4·4; S, 20·1%).

The acid (0·5 g.) and thionyl chloride were boiled for 20 minutes, and the mixture diluted with ether and slowly added to excess of ethereal aniline. The mixture was shaken with dilute hydrochloric acid and with water, dried, and evaporated. The residue of *anilide* after two crystallisations from alcohol had m. p. 172—174°, unchanged on further crystallisation from alcohol and from aqueous acetone (Found : C, 60·25; H, 3·6; N, 5·6; S, 24·4. $C_{13}H_9ONS_2$ requires C, 60·2; H, 3·5; N, 5·4; S, 24·7%).

Preparation of Thiophthencarboxylic Acid (*G*) *by Means of the Grignard Reagent.*—Thiophthen (5 g.) in dimethylaniline (60 c.c.; purified by Brand and Kranz's method, *J. pr. Chem.*, 1927, **115**, 143) was added to ethylmagnesium bromide, prepared in nitrogen from 1·11 g. of magnesium and freed from the excess of ether and ethyl bromide. The mixture was kept at 160—170°

for 1 hour in nitrogen, cooled, and treated with carbon dioxide overnight; sodium carbonate solution was then added, and unchanged thiophthen (3·37 g.) removed in steam. The liquid was filtered, acidified, and extracted with ether, giving a brownish-yellow solid (0·85 g.; m. p. 204—208° with blackening). Yield, about 12%. This was crystallised twice from carbon tetrachloride (m. p. then 216—217°) and from aqueous methyl alcohol (m. p. 219—220°) (blackening in both cases). Sublimation of a portion at 160°/13 mm. gave a whiter product of the same m. p.

An exactly similar product was obtained in a yield of 14% by the use of purified diamyl ether as solvent.

Since all these specimens of the acid blackened on melting and this was not observed with the acid (K) obtained from the ketones, further purification of the acid (G) was not attempted, the bulk being converted into derivatives, which were identical with the corresponding derivatives of the acid (K). The methyl ester prepared by means of diazomethane and crystallised from alcohol had m. p 96—96·5° alone and in admixture with the methyl ester of the acid K (Found: C, 48·5; H, 3·4; S, 32·35%). The *p*-nitrobenzyl ester, crystallised from alcohol and then from acetone, melted at 150·5—151° alone and at 151—152° in admixture with the corresponding derivative of the acid (K) (Found: C, 52·7; H, 3·0; S, 20·6%).

Thiophthendicarboxylic Acid.—Thiophthen (5 g.) in purified dimethylaniline (60 c.c.) was added to ethylmagnesium bromide prepared in nitrogen from magnesium (1·74 g.; 2 atoms.) and freed from ethyl bromide and the excess of ether. The mixture was heated in nitrogen at 200° for 45 minutes, cooled, treated with carbon dioxide overnight, decomposed with aqueous sodium carbonate, and distilled in steam, 0·65 g. of thiophthen being recovered. The red alkaline liquid was filtered, concentrated (charcoal), and acidified. The gelatinous precipitate was separated and treated with sodium carbonate solution, and the alkaline extract acidified. The dark-coloured acid thus obtained was unmelted below 300°. Extraction with hot pyridine removed much colouring matter, leaving the pyridine salt of the acid. Solution in sodium carbonate and acidification gave a greenish precipitate, which on distillation with lime evolved a strong odour of thiophthen.

This crude acid was treated with ethereal diazomethane, the solvent evaporated, and the residue crystallised from alcohol, giving short, pale yellow needles of the *dimethyl* ester, m. p. 238·5—239·5° [Found: C, 46·6; H, 3·2; S, 25·1. $C_6H_2S_2(CO_2Me)_2$ requires C, 46·85; H, 3·15; S, 25·0%. $C_6HS_2(CO_2Me)_3$ requires C, 45·8; H, 3·2; S, 20·4%].

Thiophen and Ethylmagnesium Bromide.—The Grignard solution was prepared from 3 g. of magnesium (1 atom.), volatile matter removed at 100°, and a solution of thiophen (10 c.c.) in purified dimethylaniline (120 c.c.) added. The mixture was heated at 160—170° for $1\frac{1}{4}$ hours, both operations being carried out in nitrogen. It was then cooled and treated with carbon dioxide for 1 hour. Sodium carbonate solution was added, dimethylaniline and unchanged thiophen removed in steam, the mixture acidified and extracted with ether, and the extract shaken with aqueous sodium bicarbonate. Acidification of the resulting sodium salt and extraction with ether yielded a buff-coloured solid (1·55 g.) and traces of propionic acid. The solid was boiled with alcohol (charcoal), giving a nearly colourless product, m. p. 123—125·5°, unchanged on repeated crystallisation from hot water. The acid was not pure, however, and was converted into the ethyl ester by the Fischer–Speier method. The crude product was shaken for 24 hours with concentrated aqueous ammonia (15 c.c.). The solid, m. p. 174—176°, was crystallised from chloroform to constant m. p. 176—177° (Found: N, 11·05. Calc. for C_5H_5ONS: N, 11·0%). The amide was hydrolysed with hot aqueous potassium hydroxide, the solution acidified and distilled in steam, and the volatile acid extracted with ether. After recrystallisation from water it had m. p. 125·5—126·5° (Found: C, 47·4; H, 3·55. Calc. for $C_5H_4O_2S$: C, 46·85; H, 3·15%).

Thiophen-2-carboxylic acid melts at 126·2° and the 3-isomer at 138·4° (Voerman, *Rec. Trav. chim.*, 1907, **26**, 297). The amide of thiophen-2-carboxylic acid is stated to melt at 174° by Meyer (*Annalen*, 1886, **236**, 210), at 175° by Hantzsch (*Ber.*, 1891, **24**, 48), and at 180° by Nahnsen (*Ber.*, 1884, **17**, 2196). The amide of the 3-acid melts at 177—178° (Damsky, *Ber.*, 1886, **19**, 3285).

Repetition of this experiment with four times the above quantities, heating for $1\frac{3}{4}$ hours, and treating with carbon dioxide for 1 hour gave almost the same weight of crude acid (1·26 g.), m. p. 122—123°. This was repeatedly crystallised from light petroleum, the m. p. of successive fractions being 125—125·5°, 126·5—127°, 126·9°, 127·3°, 127·5°, 127·5°. The mother-liquors yielded further quantities of acid of m. p. 126·5—127° and 125°. Finally a trace of acid, m. p. 119—121°, was left.

The 2- and the 3-carboxylic acid form mixed crystals which are almost inseparable (Voerman, *loc. cit.*, p. 293). A mixture containing about 70% of the 3-acid has a setting point about 126°, but it is improbable that such a large quantity of a 3-substitution product would be obtained from thiophen, which, so far as is known, invariably undergoes substitution in position 2. The 2-carboxylic acid would therefore appear to be exclusively formed in this reaction.

The authors thank the Institute of Petroleum and Imperial Chemical Industries for grants and the Department of Scientific and Industrial Research for a maintenance allowance to G. M. G. Dr. H. B. Gibson rendered valuable assistance in the preliminary stages of the research.

THE UNIVERSITY, LEEDS. [*Received, November* 20*th*, 1939.]