509. *Thionaphthencarboxylic Acids.*

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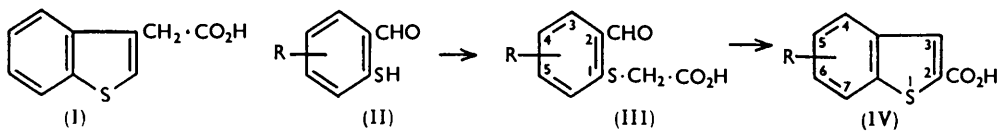
All the isomeric thionaphthencarboxylic acids, except thionaphthen-4-carboxylic acid, have been synthesised. Most of these syntheses involve intermediate formation of bromothioindoxyls by ring closure from the appropriate *ortho*-substituted (bromophenylthio)acetic acids. Ring closure was facilitated by the presence of a formyl group or its equivalent in the *ortho*-position to a carboxyl or cyano-group.

Since 3-thionaphthenylacetic acid [1] (I) has growth-promoting action on plants, attempts, interrupted by the war, have been made to prepare and test biologically all of the possible thionaphthenylacetic acids. This has been done,[2] with the exception of 4-thionaphthenylacetic acid which has been made otherwise,[3] by preparing the corresponding thionaphthencarboxylic acids (by carboxylation of the thionaphthenyl Grignard reagents) and converting these, through their diazo-ketone derivatives, into the thionaphthenylacetic acids. The Grignard process was unsuccessful with 4-bromothionaphthen, and thionaphthen-4-carboxylic acid is still unknown. The required bromothionaphthens were obtained by reduction of the corresponding thioindoxyls produced by cyclisation of (bromophenylthio)-acetic, (bromo-2-carboxyphenylthio)acetic, or (bromo-2-cyanophenylthio)acetic acids. Although there is no ambiguity in the structure of the thionaphthens made from the corresponding thioindoxyls, the yields can be very low, for reasons given by Banfield *et al.*[4] Intermediate formation of thioindoxyls was sometimes avoided by cyclising (unisolated) (*o*-formylphenylthio)acetic acids (III) or their aldimine equivalents, to give the acids (IV). It is now found that thiosalicylaldehyde (II; R = H) can be made directly in very small yield by the reduction of thiosalicylic or dithiosalicylic acid with sodium amalgam, analogously to the conversion of salicylic acid into salicylaldehyde by Weil.[5] Attention



is directed to the good yield [6] of thiosalicylaldehyde obtained by the reduction of *N*-methylthiosalicylanilide with lithium aluminium hydride. Another useful innovation is the application of Stephen's method [7] for the reduction of (*o*-cyanophenylthio)acetic acid (X; R = H) to the aldehydic acid (XI; R = H) or the corresponding imidoyl chloride. Although, because of steric hindrance, this method fails with some *ortho*-derivatives of benzonitrile,[8,9] useful yields of thionaphthen-2-carboxylic acid and 5-bromothionaphthen-2-carboxylic acid have been obtained.

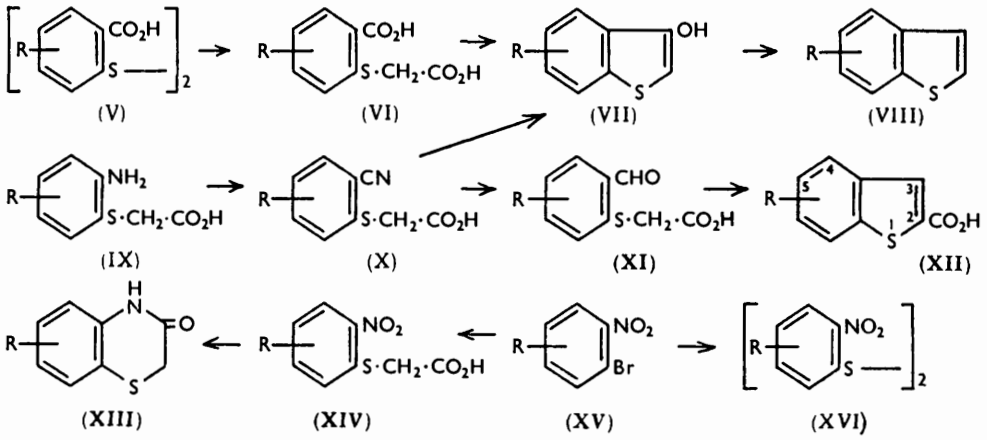
Hartough and Meisel,[9] referring to the contrast in the m. p. 114° of the thionaphthen-2-carboxylic acid obtained by the cyclisation of (*o*-formylphenylthio)acetic acid [10] (III; R = H) and m. p. 236° of the acid obtained by metallation of thionaphthen followed by

[1] Crook and Davies, *J.*, 1937, 1697; Blicke and Sheets, *J. Amer. Chem. Soc.*, 1948, **70**, 3768; Steinkopf, "Die Chemie des Thiophens," Steinkopff, Leipzig, 1941, p. 164.
[2] Kefford and Kelso, *Austral. J. Biol. Sci.*, 1957, **10**, 80.
[3] Kloetzel, Little, and Frisch, *J. Org. Chem.*, 1953, **18**, 1511.
[4] Banfield, Davies, Ennis, Middleton, and Porter, *J.*, 1956, 2603.
[5] Weil, *Ber.*, 1908, **41**, 4147.
[6] Weygand and Eberhardt, *Angew. Chem.*, 1953, **65**, 525.
[7] Stephen, *J.*, 1925, **127**, 1874.
[8] *Idem*, *J.*, 1930, 2786; King, L'Ecuyer, and Openshaw, *J.*, 1936, 352.
[9] Hartough and Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publ. Inc., New York, 1954, p. 131.
[10] Friedländer and Lenk, *Ber.*, 1912, **45**, 2083.

carboxylation,[11] suggest that the lower melting point (114°) " indicated impurity." Both of these syntheses have been repeated and thionaphthen-2-carboxylic acid is also made by the removal of the nitro-group after cyclisation of (5-nitro-2-formylphenylthio)acetic acid (III; R = 5-NO_2). In all three cases the acids had m. p. and mixed m. p. 236°. Additional evidence in favour of structure (IV; R = H) for this acid is obtained by a consideration of the different syntheses of thionaphthen-2 : 3-dicarboxylic acid. This acid is now obtained by the action of ethylmagnesium iodide and carbon dioxide on 3-bromothionaphthen, on thionaphthen-3-carboxylic acid, and on thionaphthen, and also from thionaphthen-2 : 3-quinone by repeating the method of Bezdrik, Friedländer, and Koeniger.[12] Finally, as the thionaphthen-2-carboxylic acid (m. p. 236°) was desulphurised by Blicke and Sheets [1] to the expected β-phenylpropionic acid, the m. p. 114° recorded for the acid may be due to a clerical error.

Crook and Davies [1] ascribe m. p. 174—175° to thionaphthen-3-carboxylic acid, and also describe a thionaphthenylidenediacetic acid, m. p. " about 108°." This is a clerical error for " about 208°," and the compound is probably 2 : 3-thionaphthenylenediacetic acid.

Thionaphthen-5-carboxylic acid (VIII; R = 5-CO_2H) was synthesised by carboxylation of the Grignard complex from 5-bromothionaphthen, prepared by Clemmensen reduction of 5-bromothioindoxyl. Since this method can cause some reduction of the thiophen ring and even loss of bromine, a gentler reduction with " mossy zinc " (see p. 2628) was found advisable, though even with this modification the yields of bromothionaphthen were poor. A more direct synthesis is by the decarboxylation of 5-bromothio-



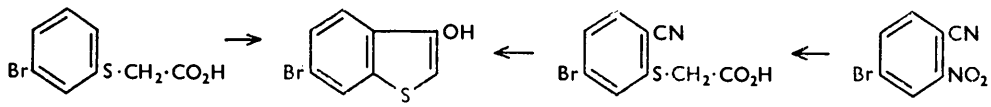
naphthen-2-carboxylic acid (XII; R = 5-Br), formed by cyclisation of (unisolated) (4-bromo-2-formylphenylthio)acetic acid (XI; R = 4-Br) or its equivalent, arising from reduction of the cyano-group in (4-bromo-2-cyanophenylthio)acetic acid (X; R = 4-Br).

The preparation of 5-bromothioindoxyl by cyclisation of (*p*-bromophenylthio)acetic acid [13] is inferior to cyclisation with acetic anhydride of (4-bromo-2-carboxyphenylthio)-acetic acid (VI; R = 4-Br), readily made from 4 : 4'-dibromodithiosalicylic acid (V; R = 4-Br) by reduction and interaction with chloroacetic acid. A better method is to start with 2 : 5-dibromonitrobenzene (XV; R = 5-Br) which with sodium disulphide gives the disulphide (XVI; R = 4-Br), easily converted into (4-bromo-2-nitrophenylthio)acetic acid (XIV; R = 4-Br); this was made in higher yield (90%) by direct interaction of the bromide (XV; R = 4-Br) with mercaptoacetic acid. Reduction of this nitro-acid gave 6-bromo-3 : 4-dihydro-3-oxo-1 : 4-benzothiazine (XIII; R = 6-Br) (also directly obtained from 4-bromo-2-nitroaniline by diazotisation and then condensation with chloroacetic

[11] Weissberger and Kruber, *Ber.*, 1920, **53**, 1561.
[12] Bezdrik, Friedländer, and Koeniger, *Ber.*, 1908, **41**, 227.
[13] Pummerer, *Ber.*, 1909, **42**, 2279.

acid and sodium disulphide, the last named reagent reducing the nitro-group). A Sandmeyer reaction on the (2-amino-4-bromophenylthio)acetic acid from this benzothiazine gave (4-bromo-2-cyanophenylthio)acetic acid (X; R = 4-Br) which, with alkali followed by acid, formed 5-bromothioindoxyl (VII; R = 5-Br).

For preparation of thionaphthen-6-carboxylic acid (VIII; R = 6-CO_2H) 6-bromothioindoxyl was obtained by cyclisation of (*m*-bromophenylthio)acetic acid. The product was identical with that synthesised unambiguously from 4-bromo-2-nitroaniline, produced by the nitration of *p*-bromoacetanilide, followed by hydrolysis, as described by Hübner.[14] In this nitration difficulty was encountered in preventing migration of the bromo-substituent,[15] so *o*-nitroaniline was brominated to give 4-bromo-2-nitroaniline,[16] which was converted into 4-bromo-2-nitrobenzonitrile (XX). Holmes and Loudon [17] have shown that the nitro-group in the analogous 4-chloro-2-nitrobenzonitrile is mobile, and similar mobility occurs with the bromo-compound, for (5-bromo-2-cyanophenylthio)acetic acid (XIX) was easily obtained from it. The above acid was then converted into 6-bromothioindoxyl (XVIII) which was reduced to 6-bromothionaphthen (VII; R = 6-Br).



(XVII) (XVIII) (XIX) (XX)

Thioindoxyl-7-carboxylic acid was obtained by cyclisation of (*o*-carboxyphenylthio)-acetyl chloride with aluminium chloride in *o*-dichlorobenzene. The yield was good and reduction in the usual way gave thionaphthen-7-carboxylic acid (VIII; R = 7-CO_2H).

Experimental

(o-*Cyanophenylthio*)*acetic Acid* (X; R = H).—*o*-Nitrochlorobenzene was converted into di-(*o*-nitrophenyl) disulphide [18] and thence by Claaz's method [19] into (*o*-nitrophenylthio)acetic acid; however, the last compound was more easily prepared by the direct reaction [20] of *o*-chloronitrobenzene with mercaptoacetic acid, as follows. *o*-Chloronitrobenzene (31·5 g.), mercaptoacetic acid (15·2 ml.), and sodium hydrogen carbonate (40 g.) in 50% aqueous alcohol (440 ml.) were refluxed for 3 hr. The alcohol was evaporated and the residue diluted with hot water. The cold solution was filtered and the filtrate on acidification gave a precipitate of (*o*-nitrophenylthio)acetic acid (XIV; R = H) which crystallised from water as light yellow needles, m. p. 164° (Claaz [19] gives m. p. 163—164°) (23·5 g.; 55%). Reduction with hydrogen sulphide and ammonia gave 3 : 4-dihydro-3-oxo-1 : 4-benzothiazine (XIII; R = H) (85%), m. p. 179° (Unger,[21] who treated bromoacetic acid with *o*-aminothiophenol, gives m. p. 179°).

A mixture of this dihydro-oxobenzothiazine (10 g.) and sodium hydroxide (12 g.) in water (50 ml.) was boiled for ½ hr. After cooling and dilution with twice its volume of ice, the solution was almost neutralised with concentrated hydrochloric acid, and sodium nitrite (6 g.) added. The solution was then added dropwise to a cold solution of concentrated hydrochloric acid (50 ml.) and water (50 ml.), neutralised (to Congo-red), and then added to an ice-cold solution of cuprocyanide complex from copper sulphate (15 g.) in water (80 ml.) with potassium cyanide (17 g.) in water (40 ml.). The cuprocyanide solution, which during the addition was kept at about pH 6, was gently heated after 1 hr. until effervescence ceased, cooled, made slightly acid to litmus with hydrochloric acid, filtered, and then strongly acidified. (*o*-Cyanophenylthio)-acetic acid (X; R = H) (6·5 g., 60%) formed light brown crystals (from water), m. p. 141° (lit., m. p. 140°, 142°).

Thionaphthen-2 : 3-*dicarboxylic Acid* (by Dr. E. M. Crook).—In preparing a relatively large

[14] Hübner, *Annalen*, 1881, **209**, 339.
[15] Cf. Griffith, *J.*, 1924, 940.
[16] Fuchs, *Monatsh.*, 1915, **36**, 139.
[17] Holmes and Loudon, *J.*, 1940, 1953.
[18] Bogert and Stull, *Org. Synth.*, Coll. Vol. I, 2nd Edn., 1944, p. 220.
[19] Claaz, *Ber.*, 1912, **45**, 2427.
[20] Friedländer and Chwala, *Monatsh.*, 1907, **28**, 250.
[21] Unger, *Ber.*, 1897, **30**, 607.

quantity of thionaphthen-3-carboxylic acid (from 10 g. of 3-bromothionaphthen) by the method of Crook and Davies [1] and prolonging the time of reaction, a benzene-insoluble acid (2 g.) was also obtained. After purification by sublimation, thionaphthen-2 : 3-dicarboxylic acid had m. p. 251° (Found : equiv., 113·5. Calc. for $C_{10}H_6O_4S$: equiv., 111). The anhydride, formed by prolonged heating with acetic anhydride, had m. p. 171°. The acid and the anhydride were identified by comparison with specimens prepared by Bezdrik, Friedländer, and Koeniger's method,[12] except that the intermediate thionaphthenquinone was made by the more convenient method of Pummerer.[22] Thionaphthen-2 : 3-dicarboxylic acid was also produced (in 10% yield) when thionaphthen-3-carboxylic acid, in ether, was heated with excess of ethyl iodide and magnesium, followed by carbon dioxide.

Thionaphthen-2-carboxylic Acid (XII; R = H).—(i) A solution of dithiosalicylic acid [23] (5 g.) and anhydrous sodium carbonate (1·8 g.) in boiling water (350 ml.) was treated with aniline (6 g.), then slowly cooled with stirring. Boric acid (5 g.), then 2% sodium amalgam (350 g.) were added with stirring during 1 hr., during which the solution was kept acid by the gradual addition of boric acid (100 g.). The red precipitate was filtered and steam-distilled from acid solution, and the distillate was run directly into an alkaline solution of sodium monochloroacetate (5 g.), which was then concentrated from 3 l. to 200 ml.; the filtered solution on acidification gave thionaphthen-2-carboxylic acid, m. p. 236° (0·5 g., 5%).

(ii) The difficulty in diazotising 5-aminothionaphthen-2-carboxylic acid (XII; R = 5-NH_2) made by the method of Fries *et al.*[24] is overcome by the following process (cf. Hodgson and Walker [25] and Hodgson and Turner [26]). Finely powdered sodium nitrite (1·87 g.) was stirred into concentrated sulphuric acid (12·4 ml.) at 0°. The temperature was raised to 70° until all the sodium nitrite had dissolved, and to the cold solution 5-aminothionaphthen-2-carboxylic acid (4 g.) in glacial acetic acid (35 ml.) was added, with stirring, at 0° during 30 min. The mixture was run into a stirred suspension of finely powdered cuprous oxide (5·8 g.) in absolute alcohol (50 ml.) during 30 min., the filtered precipitate was washed with alcohol, and the combined filtrates were concentrated and diluted with water. Thionaphthen-2-carboxylic acid (0·4 g., 11%) separated, having m. p. 236°, identical with the material obtained by the first method.

(iii) Dry hydrogen chloride was passed into a suspension of tin filings (2 g.) in anhydrous ether (10 ml.) until all had dissolved. (*o*-Cyanophenylthio)acetic acid (1 g.) in dry chloroform (15 ml.) was then added, and the solution saturated with hydrogen chloride, and then occasionally again so during a week. Then the solvent was distilled off and the residue refluxed with 18% hydrochloric acid solution (30 ml.) for 15 min., made alkaline, refluxed for 10 min., cooled, and acidified. It yielded to ether thionaphthen-2-carboxylic acid, m. p. 236° (0·2 g., 20%).

(4-Bromo-2-carboxyphenylthio)acetic Acid (VI; R = 4-Br).—Anthranilic acid (200 g.) in glacial acetic acid (1750 ml.) gave 5-bromoanthranilic acid (160 g.) when brominated essentially by the method of Wheeler and Oates; [27] this (50 g.) was diazotised and then reduced with sodium disulphide, to the dibromodithiosalicylic acid, m. p. 307° (40 g., 75%). This product was purer than that obtained (m. p. 291°) by brominating dithiosalicylic acid in acetic acid.

For the preparation of the thioacetic acid (VI; R = 4-Br), crude dibromodithiosalicylic acid (from 72 g. of 5-bromoanthranilic acid) was boiled in water (300 ml.) containing chloroacetic acid (37 g.) and sodium hydroxide (35 g.) for 2 hr. A further 12 g. of sodium hydroxide in a little water was added after a few minutes, and a similar quantity after the first hour.

(4-Bromo-2-carboxyphenylthio)acetic acid (VI; R = 4-Br) (65 g.), crystallised from water, has m. p. 215—217° (Found : equiv., 144. $C_9H_7O_4BrS$ requires equiv., 145·5). The same acid was obtained, in good yield, by interaction of chloroacetic acid in alkali with the 5-bromothiosalicylic acid made by the reduction of the dibromodithiosalicylic acid by zinc dust in acetic acid.

(4-Bromo-2-nitrophenylthio)acetic acid (XIV; R = 4-Br) was made from various starting materials. Interaction of 1 mol. of 5-bromo-2-chloronitrobenzene, 2 : 5-dibromonitrobenzene, or 5-bromo-2-iodonitrobenzene with 1 mol. of sodium disulphide in boiling alcohol for 2 hr. gave di-(4-bromo-2-nitrophenyl) disulphide (XVI; R = 4-Br) in 60, 65, and 80% yield respectively.

[22] Pummerer, *Ber.*, 1910, **43**, 1370.
[23] Allen and MacKay, *Org. Synth.*, Coll. Vol. II, 1944, p. 580.
[24] Fries, Heering, Hemmecke, and Siebert, *Annalen*, 1936, **527**, 83.
[25] Hodgson and Walker, *J.*, 1933, 1620.
[26] Hodgson and Turner, *J.*, 1942, 748.
[27] Wheeler and Oates, *J. Amer. Chem. Soc.*, 1910, **32**, 770.

These yields were all higher than that obtained by the interaction of diazotised 4-bromo-2-nitroaniline with aqueous sodium disulphide. Claaz's method [19] for preparation of (arylthio)acetic acids from disulphides was used (55% yield) but a shorter reduction time with glucose was necessary to obtain a clean product. An excellent method, however, is from 2 : 5-dibromonitrobenzene as follows.

(i) A solution of 2 : 5-dibromonitrobenzene (120 g.), mercaptoacetic acid (44 g.), and sodium hydrogen carbonate (80 g.) in 3 : 1 aqueous alcohol (2·5 l.) was refluxed for 4 hr., evaporated to one-third of its volume, diluted with hot water (9 l.), filtered, and acidified giving (*4-bromo-2-nitrophenylthio)acetic acid* (XIV; R = 4-Br), yellow plates (from alcohol) (112 g., 90%), m. p. 218° (Found: C, 33·15; H, 2·35. $C_8H_6O_4NSBr$ requires C, 32·9; H, 2·05%).

6-Bromo-3 : 4-dihydro-3-oxo-1 : 4-benzothiazine (XIII; R = 6-Br).—(i) Hydrogen sulphide was passed into a mixture of powdered (4-bromo-2-nitrophenylthio)acetic acid (135 g.) and ammonia (*d* 0·95; 4100 ml.) during a week. All the powder disssolved to give a red solution. This solution was boiled for 4 hr., filtered hot, and acidified with excess of dilute sulphuric acid, a white precipitate being formed. When the mixture was warmed, the precipitate of *6-bromo-3 : 4-dihydro-3-oxo-1 : 4-benzothiazine* (80 g., 70%) coagulated, and was then crystallised from alcohol, forming needles, m. p. 206° (Found: C, 39·1; H, 2·7. C_8H_6ONSBr requires C, 39·35; H, 2·4%).

(ii) The most direct method, involving two reducing actions of sodium disulphide, is as follows. A solution of 4-bromo-2-nitroaniline (16 g.) in concentrated hydrochloric acid (200 ml.) was poured into water (200 ml.), cooled, and diazotised by sodium nitrite (5 g.) in water (20 ml.). The filtered diazo-solution was run slowly into alkaline sodium disulphide [from crystalline sodium sulphide (38 g.), sulphur (5 g.), sodium hydroxide (8 g.), and water (100 ml.)] at <5°, then after 1 hr. at room temperature the unstable disulphide was collected and immediately dissolved in sufficient aqueous alkali for the resulting solution to be about 2N with respect to sodium hydroxide. The mixture, with a neutralised solution of chloroacetic acid (7·5 g.) in water (50 ml.), was heated on the water-bath for 2 hr. and after acidification the precipitated 6-bromo-3 : 4-dihydro-3-oxobenzothiazine (6·2 g., 31%) was crystallised, forming needles (from alcohol), m. p. 206°. It was converted into (*4-bromo-2-cyanophenylthio)acetic acid* (6·5 g., 58%), m. p. 182—183° (from water) (Found: N, 5·2. $C_9H_6O_2SNBr$ requires N, 5·15%) in the same way that 3 : 4-dihydro-3-oxo-1 : 4-benzothiazine gave (*o*-cyanophenylthio)acetic acid (p. 2626).

5-Bromothioindoxyl (VII; R = 5-Br).—(i) (*p*-Bromophenylthio)acetic acid (1·3 g.) in hot dry benzene (15 ml.) was gradually treated with phosphorus pentoxide (4 g.) and the mixture boiled for ½ hr. After 48 hr. at room temperature the benzene was removed, and the residue dissolved in ice-cold sodium hydroxide solution, acidified, and steam-distilled. The colourless 5-bromothioindoxyl (0·2 g., 16%) had the m. p. of the product recorded by Pummerer,[13] who cyclised his substance with chlorosulphonic acid.

(ii) (4-Bromo-2-carboxyphenylthio)acetic acid (10 g.) and acetic anhydride (150 ml.) were refluxed for ½ hr., and the anhydride then removed *in vacuo*. The resulting deep red liquid was hydrolysed by an excess of refluxing alcoholic sodium hydroxide for ½ hr., and 5-bromothioindoxyl, m. p. 116°, was precipitated (90% yield) on acidification.

(iii) 33% Sodium hydroxide solution (3 ml.) was added to (4-bromo-2-cyanophenylthio)-acetic acid (2 g.) in water (40 ml.), and warmed to 80° for 15 min. Sodium chloride (12 g.) was added, and the precipitated sodium salt collected, washed with brine, and then added to 5% hydrochloric acid (30 ml.), heated at 95° for 15 min., filtered, and cooled. 5-Bromothioindoxyl, m. p. 114—115°, separated (1·1 g., 65%).

As in the conversion of (*o*-cyanophenylthio)acetic acid into thionaphthen-2-carboxylic acid (p. 2627), (4-bromo-2-cyanophenylthio)acetic acid (1 g.) gave *5-bromothionaphthen-2-carboxylic acid* (0·45 g., 48%), needles (from aqueous alcohol), m. p. 235° (Found: C, 42·4; H, 2·15. $C_9H_5O_2SBr$ requires C, 42·0; H, 1·95%).

5-Bromothionaphthen (VIII; R = 5-Br).—(i) Reduction of freshly prepared 5-bromothioindoxyl (0·4 g.) was effected by 1 hour's refluxing with amalgamated "mossy zinc" [from zinc dust (3 g.), activated for a short time with hydrochloric acid, washed, then treated with aqueous mercuric chloride] and glacial acetic acid (15 ml.). The cooled solution was made strongly alkaline and the product (0·3 g., 90%) isolated by steam-distillation and crystallisation from alcohol. 5-Bromothionaphthen formed colourless plates, m. p. 47° (Rabindran, Sunthankar, and Tilak [28] give m. p. 47°) (Found: Br, 37·8. Calc. for C_8H_5BrS: Br, 37·6%).

[28] Rabindran, Sunthankar, and Tilak, *Proc. Indian Acad. Sci.*, 1952, **36**, *A*, 405.

(ii) 5-Bromothionaphthen-2-carboxylic acid (0·25 g.), quinoline (5 ml.), and copper bronze (0·05 g.) were refluxed for 1½ hr. An ether extract of the acidified solution gave 5-bromothionaphthen, m. p. 47°, in 50% yield.

Thionaphthen-5-carboxylic acid (VIII; R = 5-CO_2H), made (0·48 g., 55%) from 5-bromothionaphthen (1 g.), as in the conversion [1] of 3-bromothionaphthen into thionaphthen-3-carboxylic acid, crystallised from aqueous alcohol, or much water, in needles, m. p. 211—212° (Found: equiv., 176. $C_9H_6O_2S$ requires equiv., 178).

(m-*Bromophenylthio*)*acetic Acid* (XVII).—(i) *m*-Bromobenzenesulphonyl chloride (50 g.) was refluxed with granulated zinc (125 g.) and concentrated hydrochloric acid (250 ml.) for 2 hr., then the *m*-bromothiophenol immediately steam-distilled into an agitated solution of chloroacetic acid (20 g.) containing excess of sodium hydroxide which was next heated on the water-bath for 45 min. Acidification of the filtered solution gave (m-*bromophenylthio*)*acetic acid*, granules (from water), m. p. 87° (overall yield, 60%) (Found: equiv., 247. $C_8H_7O_2BrS$ requires equiv., 247).

(ii) Though the interaction of diazotised anthranilic acid and aqueous sodium disulphide [25] has always smoothly produced dithiosalicylic acid in some 200 repetitions of the experiment made in this Department, nevertheless explosions occurred when diazotised *m*-bromoaniline or diazotised methyl anthranilate was used. However, diazotised *m*-bromoaniline was, by the use of potassium ethyl xanthate,[29] safely converted into *m*-bromothiocresol, which with chloroacetic acid and excess of sodium hydroxide gave (*m*-bromophenylthio)acetic acid in 60% overall yield. This was also obtained, in poor yield, by the addition of diazotised *m*-bromoaniline to mercaptoacetic acid.

4-*Bromo-2-nitroaniline*.—The nitration of *p*-bromoacetanilide with a mixture of nitric and sulphuric acid gives [15] 2 : 4-dibromo-6-nitroacetanilide and it is now found that this can be a product of Hübner's process [14] in which nitric acid (*d* 1·52) alone is used. However, *o*-nitroaniline is smoothly brominated [16] to 4-bromo-2-nitroaniline, easily convertible into 4-bromo-2-nitrobenzonitrile,[30] m. p. 97°.

(5-*Bromo-2-cyanophenylthio*)*acetic Acid* (XIX).—A solution of 4-bromo-2-nitrobenzonitrile (10 g.) and mercaptoacetic acid (15 ml.) in 1 : 1 aqueous alcohol (400 ml.) was made just alkaline to phenolphthalein with sodium hydroxide solution, and sodium acetate crystals (20 g.) were added. After 12 hours' refluxing most of the solvent was distilled off; the precipitate isolated after cooling crystallised from boiling water and then from alcohol, giving (5-*bromo-2-cyanophenylthio*)*acetic acid* (6·8 g., 60%), yellow needles, m. p. 196° (Found: S, 11·6. $C_9H_6O_2NBrS$ requires S, 11·75%).

6-*Bromothioindoxyl* (XVIII).—(i) (*m*-Bromophenylthio)acetic acid (25 g.) was boiled, until interaction ceased, with excess of thionyl chloride, of which the excess was removed *in vacuo*. To the resulting unisolated acid chloride in *o*-dichlorobenzene (200 ml.) powdered aluminium chloride (16 g.) was gradually added and the temperature was finally raised to 45°, the whole reaction requiring 40 min. Ice and sodium hydroxide were added until the mixture was alkaline, and the aqueous layer after extraction with ether was acidified, to give colourless 6-*bromothioindoxyl* (14 g., 60%), m. p. 153° (from alcohol), which rapidly became pink in air (Found: Br, 35·0. C_8H_5OBrS requires Br, 34·9%).

(ii) The same product was obtained in 60% yield from (5-bromo-2-cyanophenylthio)acetic acid by treatment with alkali and then acid as described for the preparation of 5-bromothioindoxyl from (4-bromo-2-cyanophenylthio)acetic acid.

6-*Bromothionaphthen* (VIII; R = 6-Br).—Reduction of bromothioindoxyls with zinc dust and concentrated hydrochloric or acetic acid or sodium hydroxide produces poor yields of the bromothionaphthens. In one instance 6-bromothioindoxyl was refluxed with zinc dust and glacial acetic acid for 3 hr. The steam-distillate, from the reaction mixture made alkaline, yielded to ether an oil of which the more volatile fraction (b. p. 105—110°/20 mm.) contained sulphur compounds. The higher fraction contained about a 15% yield of 6-bromothionaphthen. A better yield was obtained as follows. 6-Bromothioindoxyl (6 g.) was refluxed with glacial acetic acid (50 ml.) and amalgamated " mossy " zinc (from zinc dust, 12 g.) for 50 min. with stirring and the mixture made alkaline with sodium hydroxide and steam-distilled. The distillate gave a moderate yield of 6-*bromothionaphthen*, b. p. 139—140°/30 mm., which after vacuum sublimation formed prisms, m. p. 56° (Found: S, 15·1. C_8H_5BrS requires S, 15·0%).

[29] Cf. Tarbell and Fukushima, *Org. Synth.*, 1947, **27**, 81.
[30] Claus and Scheulen, *J. prakt. Chem.*, 1891, **43**, 203.

Thionaphthen-6-carboxylic Acid.—Carboxylation of the Grignard complex, prepared from 6-bromothionaphthen as described for 5-bromothionaphthen, gave thionaphthen-6-carboxylic acid (50%) as needles, m. p. 162°, from alcohol (Found: equiv., 179·9. $C_9H_6O_2S$ requires equiv., 178).

(o-*Carboxyphenylthio*)*acetic Acid.*—This acid was prepared in 40% yield from anthranilic acid *via* dithiosalicylic acid [31] as described (p. 2627) for (4-bromo-2-carboxyphenylthio)acetic acid. The same acid has been obtained as follows. A diazotised solution, at <5°, of anthranilic acid [from anthranilic acid (7·5 g.), concentrated hydrochloric acid (10·7 ml.), and sodium nitrite (4·1 g.)] was added to mercaptoacetic acid (5 g.) in cold water (75 ml.) containing excess of sodium hydrogen carbonate, further quantities of the last being added as required to keep the solution neutral. Acidification gave the required (*o*-carboxyphenylthio)acetic acid, m. p. 214° (lit.,[32] m. p. 216—217°) in 34% yield.

Thioindoxyl-7-carboxylic Acid.—(i) (*o*-Carboxyphenylthio)acetic acid (65 g.) was converted into the acid chloride with thionyl chloride and cyclised in *o*-dichlorobenzene as for the preparation of 6-bromothioindoxyl. Thioindoxyl-7-carboxylic acid (90%) crystallised from water or aqueous alcohol in needles, m. p. 310° (Found: equiv., 193·8. $C_9H_6O_3S$ requires equiv., 194).

(ii) The acid chloride (from 0·5 g. of acid) in ether was treated with boron trifluoride (9·5 g.) in ether. After 3 days the solution was refluxed for 15 min., cooled, and extracted with dilute sodium hydroxide. Acidification of the alkaline extract gave thioindoxyl-7-carboxylic acid in 75% yield.

Thionaphthen-7-carboxylic Acid.—After reduction of thioindoxyl-7-carboxylic acid with amalgamated "mossy" zinc in boiling glacial acetic acid for ½ hr. the acetic acid was removed by steam, and thionaphthen-7-carboxylic acid crystallised from water, and then from aqueous alcohol, in needles, m. p. 172° (55%) (Found: equiv., 179. $C_9H_6O_2S$ requires equiv., 178).

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[31] D.R.P. 181,658.
[32] Friedländer, *Annalen*, 1907, **351**, 403.