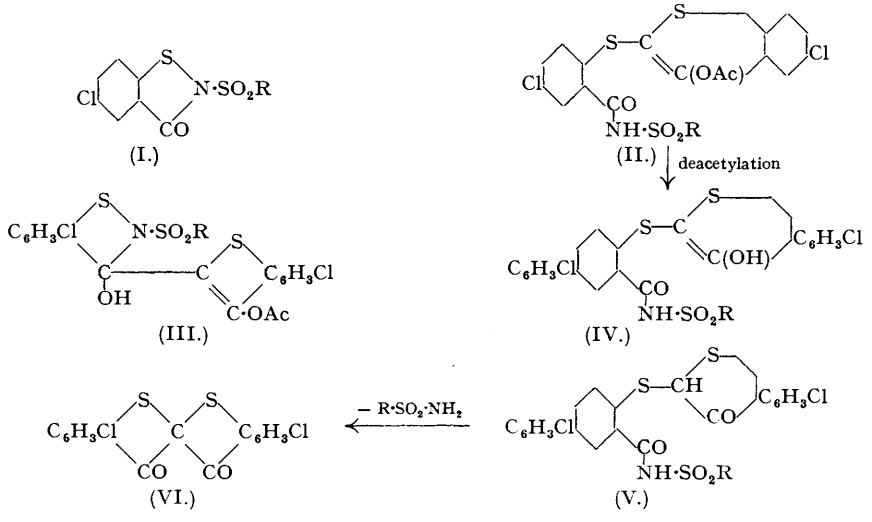
100. *The Reaction of Some Arylsulphonylbenzisothiazolones with Acetic Anhydride and Potassium Acetate.*

By F. S. Fowkes and (the late) Ernest W. McClelland.

The influence of the arylsulphonyl group and nuclear chlorine as substituents on the nature of the products obtained in the reaction of benz*iso*thiazolones with acetic anhydride and potassium acetate has been studied. It is shown that both the arylsulphonyl group and chlorine promote the condensation of hydroxythionaphthens, formed during reaction, with the unchanged benz*iso*thiazolone. The condensation products and the compounds derived from them by elimination of arylsulphonamide have been synthesised, and structures assigned to them. It is concluded that the arylsulphonyl group and nuclear chlorine both weaken the S–N bond of a benz*iso*thiazolone.

In previous communications (McClelland, J., 1929, 1588; McClelland and D'Silva, J., 1931, 2972; 1932, 2883; Bartlett and McClelland, J., 1934, 818; McClelland, Rose, and Bartlett, J., 1940, 323) it has been shown that the nature of the 1-substituent in a benz*iso*thiazolone influences the course of the reaction of these compounds with acetic anhydride and potassium acetate. The influence of the arylsulphonyl group as a substituent, with and without chlorine in the aromatic nucleus, has now been investigated. 4-Chloro-1-benzenesulphonylbenz*iso*thiazolone (I; R = Ph) on being heated with these reagents gave 5-chloro-3-acetoxy-1-thionaphthen, N-*acetylbenzenesulphonamide*, and a *substance* (A). The last, on oxidation, gave, according to the conditions used, thioindigotin or 5-chloro-3-hydroxy-1-thionaphthen 1 : 1-dioxide, the presence of a thionaphthen nucleus being therefore indicated. The product of its reaction with aniline, on the other hand, gave, when heated with nitrobenzene, the 4-*chloro*-1-*phenylbenz*iso*thiazolone* (I; Ph instead of SO_2R), showing the presence of the benz*iso*thiazolone nucleus or a structure which could readily produce it. This behaviour suggested that the compound (A) had resulted from condensation of a hydroxythionaphthen, formed by the action of acetic anhydride and potassium acetate on the benz*iso*thiazolone, with unchanged benz*iso*thiazolone. This was confirmed by the synthesis of (A) from 5-chloro-3-hydroxy-1-thionaphthen and 4-chloro-1-benzenesulphonylbenz*iso*thiazolone. These substances condensed in presence of piperidine, and the product, on acetylation, yielded (A).



Two modes of condensation of a hydroxythionaphthen with a benz*iso*thiazolone appear probable: a condensation accompanied by ring fission of the benz*iso*thiazolone or an aldol type of addition, leading respectively to the formulæ (II or III; R = Ph) for (A).

The acetyl and the benzenesulphonamido-group were eliminated from (A) by heating it with pyridine. The product, a nitrogen-free *substance* (B), was also obtained together with benzenesulphonamide when (A) was deacetylated and the resulting compound heated in toluene. It is thus evident that the removal of the benzenesulphonamido-group from (A) by pyridine is preceded by deacetylation. The ease of elimination of benzenesulphonamide from (A) by way of its deacetylation product suggests that (A) has the structure (II) and not (III), though the latter cannot be excluded entirely on the available evidence.

Deacetylation of (II) would give (IV), which could exist in the ketonic form (V), and the elimination of benzenesulphonamide from this leads to structure (VI) for (B). If, however, (A) had structure (III), the easy elimination of benzenesulphonamide by way of its deacetylation product does not appear likely, but it remains as a possibility which has not been completely disproved.

The substance (B) was obtained in the synthesis of (A) already described. It was also synthesised by condensing 5-chloro-3-acetoxy-1-thionaphthen with 4-chloro-1-acetylbenz*iso*thiazolone.

Compounds similar to (A) have not hitherto been detected among the products of the action of acetic anhydride and potassium acetate on non-chlorinated benz*iso*thiazolones, where the 1-substituent was other than arylsulphonyl. It therefore seemed of interest to determine whether their formation was dependent on the presence of chlorine or the arylsulphonyl group or both.

A non-chlorinated arylsulphonylbenz*iso*thiazolone (I; R = *p*-C_6H_4Me, H instead of Cl) gave similar results to the chloro-compound (I), yielding 3-acetoxy-1-thionaphthen, 3-hydroxy-2-acetyl-1-thionaphthen, *N*-acetyl-*p*-toluenesulphonamide, and a *substance* (C) corresponding to (A). This, like (A), was converted by deacetylation and loss of arylsulphonamide into a *compound* (D) analogous to (B). The same methods of synthesis were also successful for the non-chlorinated compounds.

It is thus evident that substitution of the benz*iso*thiazolone by chlorine is not essential to the formation of compounds of type (II), and that the arylsulphonyl group alone is effective. On the other hand, the chlorobenz*iso*thiazolone (I; H instead of SO_2R) which has no arylsulphonyl group gave a small amount of a compound of the type (II; Ac instead of SO_2R) in addition to the hydroxyacetylthionaphthen and *5-chloro-3-acetamido-1-thionaphthen*. Similar results were obtained with 4-chloro-1-acetylbenz*iso*thiazolone (I; Ac instead of SO_2R). This result suggests that chlorine in the *p*-position to sulphur has an influence similar to, but less than, that of the arylsulphonyl group in the 1-position. The condition favouring the formation of a compound of type (II) is obviously a weakening of the S–N bond in the heterocyclic nucleus. Our experiments show that this condition is caused by attachment of the arylsulphonyl group to the nitrogen atom, and to a lesser extent by the presence of chlorine in the *p*-position to the sulphur atom, the maximum effect being probably produced by the presence of both. These results are in agreement with the previous observation (Bartlett, Hart, and McClelland, J., 1939, 760) that an arylsulphonyl group facilitates the fission of the S–N bond in compounds of this type, which may be attributed to the electron-attracting properties of the sulphonyl group.

Experimental.

*Condensation of 4-Chloro-1-benzenesulphonylbenz*isothiazolone *with Acetic Anhydride and Potassium Acetate.*—Benz*iso*thiazolone (10 g.; Bartlett, Hart, and McClelland, *loc. cit.*), potassium acetate (7·5 g.), and acetic anhydride (57 c.c.) were heated together at 90° for 40 minutes, the product poured into water, and distilled in steam. The steam-distillate was extracted with ether, and the ethereal solution, after being shaken with 2N-sodium hydroxide and dried, gave on evaporation 5-chloro-3-acetoxy-1-thionaphthen (compare Fowkes and McClelland, J., 1941, 187). The residue from the steam-distillation consisted of a solid and an aqueous liquor. The latter, after concentration, gave, on extraction with ether, a substance (0·8 g.) which after purification had m. p. 126° alone or mixed with authentic *N*-acetylbenzenesulphonamide. The solid residue from the steam-distillation crystallised from acetic acid (charcoal) in colourless needles (2·2 g.), m. p. 223° (Found: C, 50·0; H, 2·8; S, 17·3. $C_{23}H_{15}O_5NCl_2S_3$ requires C, 50·0; H, 2·7; S, 17·4%). This *substance* (A) is insoluble in cold 2N-sodium hydroxide, but dissolves readily on warming. The warm alkaline solution gave thioindigotin on addition of potassium ferricyanide.

The substance (A) (0·5 g.) was heated at 100° for 1 hour in acetic acid (5 c.c.) with hydrogen peroxide (2·5 c.c.; 100-vol.), and the resulting solution concentrated under reduced pressure to 3 c.c. Phenylhydrazine (0·35 c.c.) was added, and the mixture heated at 100° for 15 minutes. The solid product, collected after cooling, crystallised from acetic acid in yellow needles, m. p. 290—292°, alone or mixed with 5-chloro-3-hydroxy-1-thionaphthen 1 : 1-dioxide phenylhydrazone (compare Fowkes and McClelland, *loc. cit.*).

The substance (A) (1 g.) was heated under reflux for 2 hours in aniline (2 c.c.), and the product poured into 2N-hydrochloric acid. The resulting tacky material solidified when stirred with alcohol, and crystallised from acetone in colourless needles, m. p. 253° (approx.). It was heated in boiling nitrobenzene for 20 minutes. The solution, on cooling, deposited a compound which, after purification from acetic acid, had m. p. 180° and gave no depression with an authentic specimen of 4-chloro-1-phenylbenz*iso*thiazolone prepared as described below.

A solution of (A) in pyridine (1 c.c. per g.), after being boiled under reflux for 2 hours and cooled, deposited the *substance* (B), which crystallised from toluene (charcoal) in yellow prisms, m. p. 266—268° (Found: C, 51·4; H, 1·8; S, 17·9. $C_{15}H_6O_2Cl_2S_2$ requires C, 51·0; H, 1·7; S, 18·1%); it is sparingly soluble in the usual organic solvents, and insoluble in hot 2N-sodium hydroxide or boiling concentrated hydrochloric acid. It reacts slowly with warm alkaline ferricyanide to give thioindigotin.

The substance (A) was deacetylated by warming with 2N-sodium hydroxide at 45° for 10 minutes. The *product*, obtained on acidifying the resulting solution, was crystallised successively from aqueous alcohol and from petroleum–benzene, and formed colourless needles of m. p. 184° (Found: C, 49·8; H, 2·7. $C_{21}H_{13}O_4NCl_2S_3$ requires C, 49·4; H, 2·5%). It yielded (A) on boiling with acetic anhydride for 2 hours. When this product of deacetylation was heated in

boiling toluene (20 parts) for 2 hours, a solid was deposited on cooling. Extraction of this with cold alcohol and evaporation of the extract gave benzenesulphonamide, and the residue insoluble in alcohol was identical with (B).

Synthesis of (A) and (B).—5-Chloro-3-hydroxy-1-thionaphthen (0·37 g.) and 4-chloro-1-benzenesulphonylbenz*iso*thiazolone (0·65 g.) were finely powdered and suspended in benzene (4 c.c.). A trace of piperidine was added, and the mixture heated under reflux for 20 minutes and cooled. The solid product was extracted with boiling alcohol. The insoluble portion was the substance (B). The extract was concentrated, and water added to the hot solution. The solid deposited on cooling was crystallised from alcohol, and finally from benzene, affording colourless needles, m. p. 182—184°, alone or mixed with the substance obtained by deacetylation of (A). (Benzenesulphonamide was isolated from the aqueous-alcoholic mother-liquor.) The substance of m. p. 184°, when heated with acetic anhydride, gave a product which, after crystallisation from acetic acid, had m. p. 223° alone or mixed with (A).

The substance (B) was obtained alone when 4-chloro-1-benzenesulphonylbenz*iso*thiazolone (0·6 g.) and 5-chloro-3-acetoxy-1-thionaphthen (0·4 g.) were heated in boiling pyridine (1·5 c.c.) for 2 hours, the product separating on cooling.

Condensation of 1-p-*Toluenesulphonylbenz*iso*thiazolone with Acetic Anhydride and Potassium Acetate.*—The condensation of this substance (Bartlett, Hart, and McClelland, *loc. cit.*) was carried out as with the 4-chlorobenzenesulphonylbenz*iso*thiazolone. Alkali washing of the ethereal extract from the steam-distillate yielded 3-hydroxy-2-acetyl-1-thionaphthen. Evaporation of the ethereal solution gave 3-acetoxy-1-thionaphthen. The residual aqueous liquor from the steam-distillation, when cooled, furnished *N*-acetyl-*p*-toluenesulphonamide, m. p. 136°, identical with a synthetic specimen prepared as described below. The *solid* (C) corresponding to (A) (II, with H instead of Cl; R = *p*-C_6H_4Me), obtained from the residue in the steam-distillation, crystallised from acetic acid (charcoal) in colourless prisms, m. p. 203° (Found : C, 58·1; H, 4·0; S, 19·1. $C_{24}H_{19}O_5NS_3$ requires C, 57·9; H, 3·8; S, 19·3%). Heated with pyridine, in the same way as (A), it gave a *substance* (D) corresponding to (B) (VI; with H instead of Cl), which crystallised from alcohol in yellow prisms, m. p. 176° (Found : C, 63·2; H, 2·9; S, 22·3. $C_{15}H_8O_2S_2$ requires C, 63·4; H, 2·8; S, 22·5%).

The substance (C), m. p. 203°, was deacetylated in the same way as (A), and the *product* crystallised from benzene in small colourless prisms, m. p. 149°, or from alcohol as a *mono-alcoholate* in colourless needles, m. p. 112° (Found : C, 57·2; H, 4·4; S, 19·2. $C_{22}H_{17}O_4NS,C_2H_6O$ requires C, 57·4; H, 4·6; S, 19·2%). When heated in a vacuum at 100° over calcium chloride, this substance lost weight corresponding to 0·93 mol. of ethyl alcohol. After two recrystallisations from benzene it had m. p. 149°. The substance decomposed in sunlight, and was oxidised to thioindigotin by alkaline ferricyanide. This deacetylated product was heated in boiling xylene for 5 hours, and the material deposited on cooling was separated by extraction with hot alcohol into an insoluble residue, the substance (D) of m. p. 176°, corresponding to (B) (VI; with H instead of Cl), and *p*-toluenesulphonamide recovered from the alcohol.

Synthesis of Compounds (C) and (D).—3-Hydroxy-1-thionaphthen (0·5 g.) and 1-*p*-toluenesulphonylbenz*iso*thiazolone (1 g.) were heated together for 45 minutes at 50° in benzene (6 c.c.) with a trace of piperidine. The substance which separated on cooling, after crystallisation from alcohol, had m. p. 112° and was identical with the compound obtained by deacetylation of (C). Heated with acetic anhydride for 15 minutes it yielded (C), m. p. 203°.

3-Acetoxy-1-thionaphthen (0·4 g.) and 1-*p*-toluenesulphonylbenz*iso*thiazolone (0·8 g.) were heated together for 1 hour at 100° in toluene (4 c.c.) with a trace of piperidine. The solid which separated on cooling was extracted with cold alcohol, from which *p*-toluenesulphonamide was obtained on evaporation. The insoluble residue, after crystallisation from toluene (charcoal), had m. p. 176° alone or mixed with (D).

Condensation of 4-*Chlorobenz*iso*thiazolone with Acetic Anhydride and Potassium Acetate.*—The chlorobenz*iso*thiazolone (4 g.) (Hart, McClelland, and Fowkes, J., 1938, 2114) was heated with potassium acetate (3·6 g.) and acetic anhydride (16 c.c.) at 105° for 15 minutes, and the product treated as in previous condensations. 5-Chloro-3-hydroxy-2-acetyl-1-thionaphthen, m. p. 166°, and 5-chloro-3-acetoxy-1-thionaphthen, m. p. 67° (compare Fowkes and McClelland, *loc. cit.*), were isolated from the steam-distillate. The solid residue was extracted with boiling alcohol (150 c.c.), leaving an insoluble portion. The alcoholic extract, on cooling, deposited 5-*chloro*-3-*acetamido*-1-*thionaphthen*, which crystallised from alcohol (charcoal) in colourless needles, m. p. 208—210° (1·25 g.) (Found : C, 53·2; H, 3·6; S, 13·6. $C_{10}H_8ONClS$ requires C, 53·2; H, 3·5; S, 14·2%). The residue insoluble in alcohol crystallised from acetic acid in colourless needles, m. p. 254°. This *compound* has a structure corresponding to (A) (II; Ac instead of SO_2R) (Found : C, 49·9; H, 2·9; S, 13·7. $C_{19}H_{13}O_4NCl_2S_2$ requires C, 50·2; H, 2·9; S, 14·1%). It was insoluble in cold sodium hydroxide, but dissolved on boiling, giving a solution which yielded a thioindigotin on addition of ferricyanide. When boiled for 2 hours in pyridine (10 parts) and poured into aqueous sulphuric acid, it gave (B).

Condensation of 4-*Chloro*-1-*acetylbenz*iso*thiazolone with Acetic Anhydride and Potassium Acetate.*—The benz*iso*thiazolone (Hart, McClelland, and Fowkes, *loc. cit.*) (0·6 g.) was heated at 100° for 20 minutes with potassium acetate (0·65 g.) and acetic anhydride (2·5 c.c.), poured into water, and distilled in steam. The distillate contained 5-chloro-3-acetoxy-1-thionaphthen and a trace of 5-chloro-2-acetyl-1-thionaphthen. The residual solid was extracted with boiling alcohol, the extract yielding 5-chloro-3-acetamido-1-thionaphthen, and the material undissolved in alcohol was the substance corresponding to (A) (II; Ac instead of SO_2R).

Condensation of 4-*Chloro*-1-*acetylbenz*iso*thiazolone with* 5-*Chloro*-3-*hydroxy*-1-*thionaphthen.*—These substances (equal mols.) were heated in boiling toluene with a trace of piperidine for 1 hour. The compound (B) separated on cooling.

4-*Chloro*-1-*phenylbenz*iso*thiazolone* (cf. McClelland and Gait, J., 1926, 921).—Aniline (6·7 g.) in pyridine (18 c.c.) was slowly added with stirring to a solution prepared by chlorinating 2-thiolbenzoic acid (10 g.) in carbon tetrachloride (80 c.c.) with ferric chloride (0·5 g.), and the precipitated material was collected and washed with 2N-hydrochloric acid. It crystallised from acetic acid in colourless plates, m. p. 179° (Found : C, 59·5; H, 3·0; S, 12·2. $C_{13}H_8ONClS$ requires C, 59·6; H, 3·1; S, 12·2%).

N-*Acetylbenzenesulphonamide.*—Benzenesulphonamide (2 g.) was heated in boiling acetic anhydride (20 c.c.) with freshly fused potassium acetate (2 g.) for 20 minutes, and the mixture poured into water. The solid *product* crystallised from aqueous acetic acid in colourless needles, m. p. 127° (Found : C, 48·5; H, 4·3. $C_8H_9O_3NS$ requires C, 48·3; H, 4·5%), considerably depressed on admixture with benzenesulphonamide. The corresponding *N*-acetyl-*p*-toluenesulphonamide, similarly prepared, had m. p. 136° (Found : C, 50·8; H, 5·0. Calc. : C, 50·7; H, 5·2%) (see Chaplin and Hunter, J., 1937, 1118).

The authors are indebted to Dr. R. G. Bartlett and Dr. L. E. Hart for preliminary experimental work, and to the Department of Scientific and Industrial Research for a grant.

KING'S COLLEGE, LONDON. [*Received, January 3rd,* 1945.]