311. *The Formation of Hydroxythionaphthens by the Interaction of Benzenesulphonylbenz*isothiazolone *and Substances containing a Reactive Methylene Group.*

By A. W. H. Barton and (the late) E. W. McClelland.

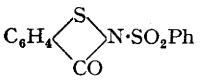
The *iso*thiazolone (I) reacts with substances containing a reactive methylene group, in presence of pyridine or piperidine, with elimination of benzenesulphonamide, to give 2-substituted derivatives of 3-hydroxythionaphthen of type (II). The group R found in the product is the acetyl, propionyl or butyryl group with the respective aliphatic ketones, and the carbethoxy-group with ketonic esters, but reaction proceeds further in the case of acetone yielding a dithionaphthenyl ketone. Benzoylacetone and acetophenone yield 3-hydroxy-2-benzoylthionaphthen. α-Picoline and quinaldine give the 3-hydroxy-2-2′-pyridyl- and -quinolyl-thio-

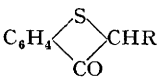
naphthen. The mechanism of the reaction is discussed, the isolation of the substance (III) as the immediate product from acetylacetone being significant.

A remarkable reaction also occurs when the *iso*thiazolone is heated with ethyl phenylacetate and pyridine or quinoline, pyridyl- or quinolyl-thionaphthen being produced.

THE work of Smiles and his collaborators (*J.*, 1912, **101**, 570; 1915, **107**, 1378; 1921, **119**, 1810; 1924, **125**, 876) showed that 3-hydroxythionaphthen and certain of its 2-derivatives could be prepared by warming together in sulphuric acid *o*-mercaptobenzoic acid and various substances such as malonic and acetoacetic esters, β-diketones, and malic or citric acid. The yields are, however, not always satisfactory, tarry by-products and thioindigotin being often present, and the reaction sometimes fails owing to the prior decomposition of the diketonic reagent.

It has now been found that the readily accessible benzenesulphonylben*zis*othiazolone (I) reacts smoothly with various substances containing a reactive methylene group to produce good yields of 2-substituted derivatives of 3-hydroxythionaphthen (II), benzenesulphonamide being simultaneously eliminated.


(I.)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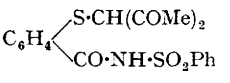
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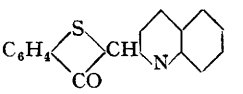

(IV.)

The reaction with ethyl malonate, ethyl acetoacetate, or ethyl acetonedicarboxylate in presence of pyridine or piperidine gives 3-hydroxy-2-carbethoxythionaphthen (II, R = CO_2Et). When the thiazolone is heated with acetylacetone in boiling alcohol or toluene in the absence of any basic catalyst, a direct *addition compound* (III) results, which is converted by the action of alkalis or by heating in boiling pyridine into 3-hydroxy-2-acetylthionaphthen (II, R = COMe) and benzenesulphonamide: this same acetylthionaphthen is obtained directly when the original reaction with acetylacetone is conducted in boiling pyridine solution. The properties of the addition compound are consistent with structure (III), which is also supported by the analogy with the products of addition of the benz*iso*thiazolone to aromatic amines, whose structure has been firmly established (McClelland and Peters, this vol., p. 1229).

From benzoylacetone the corresponding 3-hydroxy-2-benzoylthionaphthen (II, R = COPh) is formed.

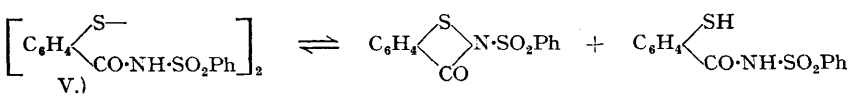
A reaction of the same kind takes place with ketones in general, but only in the presence of piperidine as catalyst. For instance, methyl ethyl ketone yields 3-hydroxy-2-propionylthionaphthen previously described by Krollpfeifer and Schneider (*Ber.*, 1928, **61**, 1284), methyl *n*-propyl ketone gives 3-*hydroxy*-2-*butyrylthionaphthen*, and acetophenone the corresponding benzoylthionaphthen, while *m*-nitroacetophenone gives 3-*hydroxy*-2-m-*nitrobenzoylthionaphthen*.

With acetone the main product is 3 : 3′-dihydroxy-2 : 2′-dithionaphthenyl ketone (compare Friedländer and Risse, *Ber.*, 1914, **47**, 1928) but a small amount of 3-hydroxy-2-acetylthionaphthen is obtained and may be an intermediate in the process. The latter substance does in fact condense further with the benz*iso*thiazolone under the conditions of the reaction.

The reaction with diethyl ketone gave 3-hydroxy-2-methylthionaphthen, identified in the form of its oxidation product 2 : 2′-bis-(3-hydroxy-2-methylthionaphthen) (compare McClelland and D'Silva, *J.*, 1931, 2972), together with some 3-hydroxy-2-propionylthionaphthen, the formation of which seems inexplicable unless it was due to the presence of methyl ethyl ketone as an impurity.

Quinaldine and α-picoline also condense with benzenesulphonylben*zis*othiazolone, yielding 3-*hydroxy*-2-2′-*quinolylthionaphthen* (IV), and the analogous *pyridylthionaphthen*.

Benz*iso*thiazolone itself did not react with boiling acetone and its reaction with methyl ethyl ketone and quinaldine was slow. The benz*iso*thiazolone when heated alone in boiling pyridine was reduced to di-*N*-benzenesulphonyl-2 : 2′-dithiobenzamide (V), and when the main condensation was slow (*e.g.*, with diethyl ketone) this disulphide (V) was sometimes found as a by-product. According to the dismutation theory (McClelland and Warren, *J.*, 1930, 1095; D'Silva and McClelland, *J.*, 1932, 2883) the disulphide and the benz*iso*thiazolone are reversibly interconvertible thus:


(V.)

It was found, in fact, that the dithiobenzamide (V) also condensed with acetylacetone slowly in boiling alcohol and somewhat faster in boiling pyridine.

No reaction could be detected between benzenesulphonylbenz*iso*thiazolone and ethyl phenylacetate at 170° in presence of piperidine, but when pure quinoline was also present 3-hydroxy-2-2′-quinolylthionaphthen resulted, and with pyridine the analogous pyridylthionaphthen was again produced. These products were formed only when all three reactants were present, but the result has not been explained. When dimethylaniline was substituted for quinoline, an intensely blue substance was found in addition to 2-*N*-benzenesulphonylcarbamyl-4′-dimethylaminodiphenyl sulphide (cf. McClelland and Peters, *loc. cit.*), but its nature has not been elucidated.

Experimental.

*Reactions of Benzenesulphonylbenz*isothiazolone *with Ketonic Substances.—Acetylacetone.* The benz*iso*thiazolone (5 g.) was heated in boiling ethyl alcohol (70 c.c.) with acetylacetone (3 g.) for 2 hours. On cooling, 3-(2′-*benzenesulphonylcarbamylphenyl*-1′-*thio*)*pentane*-2 : 4-*dione* (III) crystallised out (yield 94%). It forms white plates, m. p. 163° (decomp.) (Found: C, 55·1; H, 4·4; S, 16·6. $C_{15}H_{17}O_5NS_2$ requires C, 55·2; H, 4·4; S, 16·4%). This substance gives a red coloration with ferric chloride. It is soluble in benzene or hot methyl or ethyl alcohol but insoluble in ether or hot water. It was unchanged by heating in boiling toluene for 6 hours. Attempts to methylate, acetylate, or dehydrate it were unsuccessful. It dissolves in cold aqueous sodium hydroxide and is reprecipitated unchanged on acidification. After the alkaline solution had been boiled for ½ hour it contained a thionaphthen, as shown by the formation of thioindigotin with potassium ferricyanide, and distillation of the solution in a current of steam yielded 3-hydroxy-2-acetylthionaphthen (m. p. 79°, not depressed by admixture of an authentic specimen), which was converted by phenylhydrazine into 1-phenyl-3-methyl-4 : 5-thionaphthenopyrazole, m. p. 120° (cf. Barry and McClelland, *J.*, 1935, 472). Benzenesulphonamide was deposited from the solution on cooling.

The addition compound yielded the same acetylthionaphthen when boiled in pyridine for 2 hours or heated at 40° for 4 hours with concentrated sulphuric acid.

Good yields of the same product were obtained direct by heating the benz*iso*thiazolone with acetylacetone in pyridine for 3 hours.

The corresponding reaction of 1-*p*-toluenesulphonylbenz*iso*thiazolone with acetylacetone in alcohol yielded 3-(2′-p-*toluenesulphonylcarbamylphenyl*-1′-*thio*)*pentane*-2 : 4-*dione*, white plates, m. p. 180° (decomp.), from alcohol (Found: C, 56·4; H, 4·6. $C_{19}H_{19}O_5NS_2$ requires C, 56·3; H, 4·7%), which on being heated in pyridine gave the 3-hydroxy-2-acetylthionaphthen and *p*-toluenesulphonamide.

Condensation of the benz*iso*thiazolone with the diketonic substances, with pyruvic acid, and with *m*-nitroacetophenone was carried out by boiling equimolecular quantities together in pyridine. The reaction with ketones (4—6 mols., or an excess as solvent) took place in presence of a few drops of piperidine, the ketone itself or chloroform being used as solvent. Benzenesulphonamide was isolated as a by-product in every case.

Ethyl malonate. This did not react with the thiazolone in the absence of a basic catalyst. The mixture, after 4 hours' heating in boiling pyridine, was poured into dilute acid. The precipitated oil solidified, and was distilled in a current of steam. 3-Hydroxy-2-carbethoxythionaphthen was thus isolated (yield 79%); it separated from alcohol in white plates, m. p. 74° (Found: C, 58·9; H, 4·2. Calc.: C, 59·5; H, 4·5%) (cf. Arndt, Hirsch, and Nachtwey, *Ber.*, 1926, **59**, 1077). Hydrolysis by 2N-sodium hydroxide at 100° yielded 3-hydroxythionaphthen, m. p. 70°, further converted into the thionaphthindole of m. p. 251° (McClelland and D'Silva, *J.*, 1932, 229).

Ethyl acetoacetate. This ester gave 3-hydroxy-2-carbethoxythionaphthen (yield 80%). When this was distilled in steam, a tarry residue was left from which cold alcohol separated some yellow 3 : 5′-dihydroxy-1 : 1′-dithionaphthenyl ketone which constitutes the main product from acetone.

When the reaction was carried out in ethyl alcohol with a little pyridine as catalyst the carbethoxythionaphthen and unchanged thiazolone were alone isolated, showing that the intermediate compound is unstable under these conditions.

Benzoyl acetone. The reaction mixture after 6 hours' boiling in pyridine was poured into dilute acid. The solid precipitated was distilled in a current of steam, to remove unchanged diketone, and then extracted with hot alcohol, from which 3-hydroxy-2-benzoylthionaphthen was deposited in yellow needles, m. p. 116 (Smiles and Ghosh, *J.*, 1915, **107**, 1378).

Acetone. When the benz*iso*thiazolone had been heated in boiling acetone with 2 drops of piperidine for 4 hours, yellow needles, m. p. 234°, were deposited which were identified as 3 : 3′-dihydroxy-2 : 2′-dithionaphthenyl ketone (Friedlander and Risse, *loc. cit.*) (Found: C, 62·7; H, 3·2; S, 19·6. Calc.: C, 62·6; H, 3·1; S, 19·7%), giving the diacetyl derivative, m. p. 183° (Found: C, 61·2; H, 3·3. Calc.: C, 61·5; H, 3·4%). A little 3-hydroxy-2-acetylthionaphthen was also found.

When the benz*iso*thiazolone (2 g.) was heated in boiling benzene (100 c.c.) with the hydroxyacetylthionaphthen (1·5 g.) and 2 drops of piperidine for 7 hours the same dithionaphthenyl ketone was produced (yield 68%).

Methyl ethyl ketone. Under similar conditions this ketone furnished 3-hydroxy-2-propionylthionaphthen, m. p. 74° (Krollpfeifer and Schneider, *loc. cit.*) (Found: C, 64·3; H, 5·1. Calc.: C, 64·1; H, 4·9%) (yield 57%, but this was improved by warming the mixture for 5 minutes and keeping it for 10 days).

Methyl n-*propyl ketone.* The benz*iso*thiazolone was boiled with the ketone and 6 drops of piperidine in chloroform solution for 7 hours. The mixture was diluted with ether, the solution washed successively with dilute acid and water, and evaporated. When the residue was distilled in a current of steam, the oil which came over solidified, and the 3-*hydroxy*-2-n-*butyrylthionaphthen* crystallised from

methyl alcohol in white needles, m. p. 36° (Found: C, 65·5; H, 5·7. $C_{12}H_{12}O_2S$ requires C, 65·5; H, 5·5%). This substance is slightly soluble in aqueous sodium hydroxide and slowly gives thioindigotin on shaking with alkaline ferricyanide. It gives a greenish-violet ferric chloride reaction. This and the preceding propionyl compound failed to react with phenylhydrazine in boiling alcohol in presence of a little sulphuric acid after 6 hours' heating.

Acetophenone. After the reaction, the excess of ketone was removed in a current of steam. The residue was 3-hydroxy-2-benzoylthionaphthen, crystallising from alcohol in pale yellow needles, m. p. 117° (Smiles and Ghosh, *loc. cit.*).

Pyruvic acid. The product from the condensation, isolated by pouring into acid and collecting the precipitate, was 3-hydroxythionaphthenyl-2-glyoxylic acid, yellow plates, m. p. 174°, after drying at 100° (Hart and Smiles, *J.*, 1924, **125**, 876).

m-*Nitroacetophenone.* After 6 hours' boiling of the reaction mixture, the product crystallised on cooling. It was collected, and washed with pyridine, dilute acid, and water. 3-*Hydroxy*-2-m-*nitrobenzoylthionaphthen* crystallises from alcohol in pale yellow needles, m. p. 203° (Found: C, 60·0; H, 2·9; N, 5·1. $C_{15}H_9O_4NS$ requires C, 60·2; H, 3·0; N, 4·7%).

Diethyl ketone. The thiazolone was heated for 12 hours in boiling diethyl ketone with a little piperidine, the solvent evaporated, and the residue distilled in steam. The oil which slowly distilled was collected in ether, dried (Na_2SO_4), and the solvent evaporated. 3-Hydroxy-2-methylthionaphthen was thus isolated as a yellow viscous oil soluble in aqueous sodium hydroxide. It was converted by hot alkaline ferricyanide into 2 : 2′-bis-(3-hydroxy-2-methylthionaphthen), m. p. 151° (cf. McClelland and D'Silva, *loc. cit.*), and by hydrogen peroxide in glacial acetic acid into the dioxide, m. p. 110°. Further steam distillation after acidification of the mixture yielded a little 3-hydroxy-2-propionylthionaphthen, m. p. 70°, while benzenesulphonamide and di-*N*-benzenesulphonyl-2 : 2′-dithiobenzamide, m. p. 226°, were found in the mother-liquor.

Ethyl acetonedicarboxylate. This ester condensed with the benz*iso*thiazolone on boiling in chloroform for 7 hours with a little piperidine. The solution was evaporated, and the residue acidified and distilled in a current of steam, whereupon 3-hydroxy-2-carbethoxythionaphthen came over (yield 86%).

*Reaction of Benzenesulphonylbenziso**thiazolone with Quinaldine and α-Picoline.*—The thiazolone (4 g.) was boiled in chloroform (30 c.c.) for 6 hours with quinaldine (4 g.) and 2 drops of piperidine, the solution evaporated, and the excess of base removed in a current of steam. The remaining solid (yield 92%) was 3-*hydroxy*-2-2′-*quinolylthionaphthen* (IV), which crystallised from benzene in ruby-red prisms, m. p. 184° (Found: C, 73·6; H, 4·1; N, 5·2. $C_{17}H_{11}ONS$ requires C, 73·6; H, 4·0; N, 5·1%). Similar results but lower yields were obtained by using pyridine or glacial acetic acid as solvent. This substance is soluble in alcohol, chloroform, or hot acetic acid, giving blood-red solutions. It turns yellow with alkali or concentrated mineral acids, dissolving in the latter. Hydrochloric acid produced an unstable yellow substance, m. p. 117°, presumably a hydrochloride, which was reconverted into the parent substance by water.

Oxidation with ferricyanide in piperidine solution produced a white amorphous solid (purified from hot nitrobenzene) of m. p. 273° (sublimes). This is 2 : 2′-*bis*-(3-*keto*-2-2′-*quinolylthionaphthen*) (Found: C, 73·7; H, 3·8. $C_{34}H_{20}O_2N_2S_2$ requires C, 73·9; H, 3·6%). The *acetyl* derivative of (IV) forms white plates, m. p. 177°, from acetic anhydride (Found: C, 71·4; H, 4·0. $C_{19}H_{13}O_2NS$ requires C, 71·5; H, 4·1%) and is hydrolysed rapidly by acids or alkalis and slowly by water or boiling alcohol.

The thiazolone was boiled with half its weight of α-picoline in glacial acetic acid for 5 hours. The product, which separated on cooling (yield 83%), crystallised from alcohol in fawn needles, m. p. 132°, of 3-*hydroxy*-2-2′-*pyridylthionaphthen* (Found: C, 68·8; H, 3·9. $C_{13}H_9ONS$ requires C, 68·7; H, 4·0%). A similar result was obtained by heating the thiazolone with α-picoline hydrochloride in boiling pyridine, but when the reagents were heated in chloroform with piperidine or in picoline alone as solvent the product was di-*N*-benzenesulphonyl-2 : 2′-dithiobenzamide.

The hydroxypyridylthionaphthen is soluble in hot alcohol or acetic acid or hot aqueous sodium hydroxide. It gives a yellow solution in mineral acids. It is slightly volatile in steam. Its *acetyl* derivative crystallises from acetic anhydride in massive white prisms, m. p. 133° (considerably depressed by adding the parent substance) (Found: C, 66·9; H, 4·0. $C_{15}H_{11}O_2NS$ requires C, 66·9; H, 4·1%).

*Reaction of Unsubstituted Benziso**thiazolone with Ketones and Quinaldine.*—No reaction was detected when benz*iso*thiazolone was boiled for 12 hours in acetone in presence of piperidine. With methyl ethyl ketone a very little hydroxypropionylthionaphthen was formed. With quinaldine after 8 hours' boiling in glacial acetic acid the hydroxyquinolylthionaphthen was produced in 32% yield.

Condensation with Ethyl Phenylacetate.—This ester (10 g.) would not react with benzenesulphonylbenz*iso*thiazolone (5 g.) in presence of piperidine at 170°, but when pure quinoline (10 g.) was also present reaction had occurred after 5 hours' heating. The excess of reagents and solvent was removed from the red mixture in a current of steam, and the tarry product extracted with hot aqueous sodium hydroxide. The solution was decanted, cooled, and saturated with carbon dioxide. The red precipitate proved to be 3-hydroxy-2-2′-quinolylthionaphthen, m. p. 189° (yield 42%), and benzenesulphonamide was present in the mother-liquors.

In the same way benzenesulphonylbenz*iso*thiazolone, heated with an equal weight of ethyl phenylacetate in boiling pure pyridine for 7 hours, gave 3-hydroxy-2-2′-pyridylthionaphthen, m. p. 133° (yield 39%), and the benzenesulphonyldithiobenzamide. No hydroxyphenylthionaphthen could be detected in these reactions.

The benzenesulphonylbenz*iso*thiazolone also reacted when heated for 5 hours at 170° with ethyl phenylacetate and dimethylaniline in presence of piperidine. The products isolated immediately were benzenesulphonamide, the benzenesulphonyldithiobenzamide, 2-*N*-benzenesulphonylcarbamyl-4′-dimethylaminodiphenyl sulphide, m. p. 172°, and an intensely blue substance remained in the mother-liquor. This was collected chromatographically on anhydrous alumina, removed in alcohol, and recovered as a blue solid which separates from chloroform–petroleum in blue plates with a golden iridescence, m. p. 198°. It is stable to alkalis, gives yellow solutions in acids, and with hydrogen peroxide

in acetic acid yields a substance of m. p. 214°. The formation of this blue compound requires the presence of the thiazolone, the ester, the dimethylaniline, and the catalyst, but it was also observed when 2 : 2′-dithiobenzoic acid replaced the first of these or when benzyl cyanide replaced the ester.

Di-N-benzenesulphonyl-2 : 2′-dithiobenzamide as a Possible Intermediate in the Reactions.—Benzenesulphonylbenz*iso*thiazolone, boiled for 2 hours in pyridine, gave the dithiobenzamide, m. p. 226° (yield 60%).

The dithiobenzamide (0·5 g.), heated for 2 hours in boiling alcohol with acetylacetone (0·3 g.), gave, in addition to some recovered dithiobenzamide, 3-(2′-benzenesulphonylcarbamylphenyl-1′-thio)pentane-2 : 4-dione, m. p. 163° (yield 29%).

The dithiobenzamide, heated in boiling pyridine for 3 hours with acetylacetone (2 mols.), gave 3-hydroxy-2-acetylthionaphthen (yield 44%) and benzenesulphonamide.

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