66. *The Reaction of Some Acylbenzisothiazolones with Acetic Anhydride and Potassium Acetate.*

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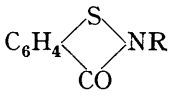
The reaction of 1-acylbenz*iso*thiazolones with acetic anhydride and potassium acetate is shown to give mixtures of thionaphthens, from which 3-hydroxy-2-acetyl-1-thionaphthen, 3-acetoxy-1-thionaphthen, 3-*hydroxy*-2-*acetylcarbamyl*-1-*thionaphthen*, and 3-acylamido-1-thionaphthenes have been isolated. Total or partial displacement of the 1-substituent by acetyl takes place, which is in contrast to the behaviour of the 1-alkyl- or 1-aryl-benz*iso*thiazolones. 3-Hydroxy-2-acetylcarbamyl-1-thionaphthen, which has been synthesised from 2-thiolbenzoic acid, has also been obtained from the unsubstituted benz*iso*thiazolone and it is shown to be a source of the acetyl hydroxy-thionaphthens.

It has been shown (McClelland, J., 1929, 1588; McClelland and D'Silva, J., 1931, 2972; 1932, 2883; Bartlett and McClelland, J., 1934, 818) that benz*iso*thiazolone (I; R = H) reacts with acetic anhydride and potassium acetate to give 3-acetamido-1-thionaphthen (II; R = Ac), whereas the 1-alkyl- or 1-aryl-substituted benz*iso*thiazolones (I; R = Me, Et, CH_2Ph or Ph) yield the 3-hydroxy-2-carbamyl-1-thionaphthens (III) and not the expected *N*-substituted aminothionaphthens (II). In these reactions 3-hydroxy-2-acetyl-1-thionaphthen (V) and 3-acetoxy-1-thionaphthen (VI) were also obtained. It was thus

evident that the nature of the 1-substituent in the benz*iso*thiazolone influenced the course of the reaction; the influence of acyl groups as the 1-substituent has now been investigated.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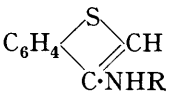
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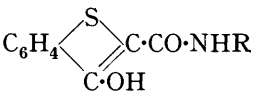
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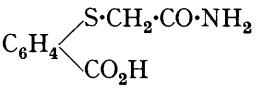
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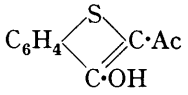
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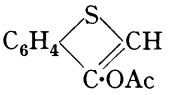
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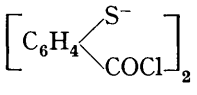
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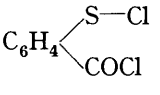
(VIII.)

1-*Propionylbenz*iso*thiazolone* (I; R = CO·C_2H_5) reacts with acetic anhydride and potassium acetate on heating to give 3-hydroxy-2-acetyl-1-thionaphthen (V), 3-acetoxy-1-thionaphthen (VI), 3-acetamido-1-thionaphthen (II; R = Ac), 3-*propionamido*-1-*thionaphthen* (II; R = CO·C_2H_5), and 3-*hydroxy*-2-*acetylcarbamyl*-1-*thionaphthen* (III; R = Ac). It is evident that displacement of the 1-propionyl group by acetyl takes place at some stage in the reaction and is incomplete as shown by the isolation of 3-propionamide-1-thionaphthen. The fact that the propionyl group was not displaced from 3-propionamido-1-thionaphthen by further heating with acetic anhydride and potassium acetate suggests that the displacement takes place at the initial stage. Attempts to isolate 1-acetylbenz*iso*thiazolone by heating 1-propionylbenz*iso*thiazolone with these reactants at various temperatures were unsuccessful, the material either being recovered unchanged or undergoing the reaction described. When, however, 1-*chloroacetylbenz*iso*thiazolone* (I; R = CO·CH_2Cl) was heated with the reactants at 70°, displacement took place with formation of 1-acetylbenz*iso*thiazolone, thus confirming that the displacement of the 1-substituent takes place in the benz*iso*thiazolone and not at some subsequent stage. Condensation at 95° gave 3-hydroxy-2-acetylcarbamyl-1-thionaphthen; at 115°, 3-acetamido-1-thionaphthen was obtained in addition to 3-hydroxy-2-acetyl-1-thionaphthen. It appears that raising the temperature favours the formation of the acetamidothionaphthen at the expense of the acetylcarbamylthionaphthen.

The benzoyl derivative (I; R = Bz) reacts with acetic anhydride and potassium acetate in a similar way to the propionyl derivative, yielding 3-hydroxy-2-acetyl-1-thionaphthen, 3-acetoxy-1-thionaphthen, 3-hydroxy-2-acetylcarbamyl-1-thionaphthen, 3-acetamido- and 3-benzamido-1-thionaphthen (II; R = Bz). The last was identified by means of its 2-nitro-derivative.

The phenylacetyl derivative (I; R = CO·CH_2Ph) yielded under similar conditions 3-hydroxy-2-acetyl-1-thionaphthen, 3-*phenylacetamido*-1-*thionaphthen* (II; R = CO·CH_2Ph) and 3-hydroxy-2-acetylcarbamyl-1-thionaphthen.

3-Acetoxy-1-thionaphthen was not identified as a product of either the chloroacetyl or the phenylacetyl derivative. A trace of an alkali-insoluble oil was obtained with similar properties, but it did not appear to give acetanilide with aniline (compare McClelland and D'Silva, *loc. cit.*). It is concluded that, if 3-acetoxy-1-thionaphthen was formed, it was present in only very small amounts.

The formation of 3-hydroxy-2-acetylcarbamyl-1-thionaphthen (III; R = Ac) is common to these reactions. Further investigation of the action of acetic anhydride and potassium acetate on the unsubstituted benz*iso*thiazolone (I; R = H) has led to the isolation of the acetylcarbamylthionaphthen from this source also. It is noteworthy that, when the condensation was effected at 70°, 3-hydroxy-2-acetylcarbamyl-1-thionaphthen was obtained in greater quantity than 3-acetamido-1-thionaphthen, whereas at 110° the 3-acetamido-1-thionaphthen was formed in excess. The observation, made in the case of the chloroacetyl derivative, that the higher temperature favours the formation of the acetamidothionaphthen is thus confirmed.

The structure assigned to 3-hydroxy-2-acetylcarbamyl-1-thionaphthen has been confirmed by its synthesis and reactions. 2-Thiolbenzoic acid was condensed with chloro-

acetamide, giving 2-*carboxyphenylthiolacetamide* (IV), which, heated with acetic anhydride, gave 3-hydroxy-2-acetylcarbamyl-1-thionaphthen. The substance gives an *acetyl* derivative (III; R = Ac; AcO instead of OH) and is hydrolysed by aqueous alkali at room temperature to 2-carbamy-1-thionaphthen (III; R = H). More vigorous hydrolysis by boiling with alkali gives 3-hydroxy-1-thionaphthen and ammonia.

3-Hydroxy-2-acetylcarbamyl-1-thionaphthen reacts with acetic anhydride and potassium acetate to give a mixture of 3-hydroxy-2-acetyl-1-thionaphthen and 3-acetoxy-1-thionaphthen, which suggests that these thionaphthen derivatives are at least partly derived from this source in the reaction of a benz*iso*thiazolone with acetic anhydride and potassium acetate.

Comparison of the results obtained in the acylbenz*iso*thiazolone series with those in the alkyl- or aryl-benz*iso*thiazolone series shows a marked similarity. In both series the benz*iso*thiazolone is transformed into hydroxythionaphthen derivatives of the types (III, V, VI). In the alkyl or aryl series the radical attached to the nitrogen of the benz*iso*thiazolone is not displaced, whereas in the acyl series the radical is wholly or partly displaced by acetyl. In the alkyl or aryl series aminothionaphthens of the type (II) have not been isolated, but the possibility of their formation cannot be excluded.

The requisite 1-acylbenz*iso*thiazolones were prepared by direct acylation of benz*iso*thiazolone. In order to confirm that the benz*iso*thiazolones prepared in this way were the *N*-derivatives and not the *O*-derivatives they were also prepared by chlorinating 2 : 2′-dithiobenzoyl chloride (VII) and condensing the product (VIII) with the appropriate amide. The acylbenz*iso*thiazolones obtained by either method were identical.

3-Propionamido-1-thionaphthen (II; R = $CO{\cdot}C_2H_5$) required for comparison in the above investigation was prepared by direct propionylation of 3-amino-1-thionaphthen. Like the corresponding acetyl derivative (compare McClelland; McClelland and D'Silva) it yields a 2-*nitro*- and a 2-*bromo*-derivative. The 2-nitro-derivatives of 3-benzamido-1-thionaphthen and 3-phenylacetamido-1-thionaphthen have also been prepared.

Experimental.

1-*Propionylbenz*iso*thiazolone* (I; R = $CO{\cdot}C_2H_5$).—Benz*iso*thiazolone (2 g.) and propionic anhydride (10 c.c.) were heated for 1 hour at 100°. The *product*, which separated on cooling, crystallised from alcohol in white plates, m. p. 144° (Found: C, 57·7; H, 4·7. $C_{10}H_9O_2NS$ requires C, 57·9; H, 4·4%).

1-*Chloroacetylbenz*iso*thiazolone* (I; R = $CO{\cdot}CH_2Cl$), obtained by heating benz*iso*thiazolone (1 g.) and chloroacetic anhydride (1 g.) for 2 hours at 100°, crystallised from alcohol in yellow needles, m. p. 171° (Found: C, 47·2; H, 2·9. $C_9H_6O_2NClS$ requires C, 47·5; H, 2·6%). 1-Chloroacetylbenz*iso*thiazolone (0·5 g.) was refluxed with acetic acid (3 c.c.) for 30 minutes; 1-acetylbenz*iso*thiazolone separated on addition of water to the solution.

1-*Phenylacetylbenz*iso*thiazolone* (I; R = $CO{\cdot}CH_2Ph$) was obtained when phenylacetyl chloride (2 c.c.) was added to a solution of benz*iso*thiazolone (2 g.) in pyridine (5 c.c.) at 0°, and the precipitated material washed with 2N-hydrochloric acid. It crystallised from alcohol in white plates, m. p. 137° (Found: C, 67·1; H, 4·1. $C_{15}H_{11}O_2NS$ requires C, 66·9; H, 4·1%).

The above 1-acylbenz*iso*thiazolones were also obtained as follows: Chlorine was bubbled through a suspension of 2 : 2′-dithiobenzoyl chloride (10 g.) in carbon tetrachloride (80 c.c.). Excess of chlorine was removed by nitrogen, and the solution added to the appropriate amide (1·2 mols.) dissolved in about three times its weight of pyridine. The required 1-acylbenz*iso*thiazolone was precipitated by the addition of 2N-hydrochloric acid. 1-Benzoylbenz*iso*thiazolone prepared by this method had m. p. 170° alone or mixed with a specimen prepared by the method of Reissert and Manns (*Ber.*, 1928, **61**, 1308).

*Condensation of the Acylbenz*iso*thiazolones with Acetic Anhydride and Potassium Acetate.*—The acylbenz*iso*thiazolone in lots of 2 g., freshly fused potassium acetate (2·5 mols.), and acetic anhydride (10 mols.) were heated together at various temperatures and for different times as indicated. The product was poured into water and distilled in steam. The steam-distillate was extracted with ether, and the ethereal solution extracted with 2N-sodium hydroxide. Acidification of the alkaline extract gave the 3-hydroxy-2-acetyl-1-thionaphthen. Evaporation of the ethereal solution gave 3-acetoxy-1-thionaphthen unless otherwise stated. The treatment of the residue after steam-distillation varied with individual cases as follows:

Reaction of 1-*propionylbenz*isothiazolone. At 115° for 15 minutes. The residue after steam-distillation consisted of a tarry material and an aqueous liquor, which were separated. The tarry material was extracted three times with successive quantities (5 c.c.) of hot acetic acid. The solids deposited from the cooled extracts were washed with aqueous sodium carbonate. The residue insoluble in sodium carbonate from the first extract after purification from benzene was identified as 3-acetamido-1-thionaphthen. The residue insoluble in sodium carbonate from the third extract was purified from aqueous acetic acid and was identical with 3-propionamido-1-thionaphthen prepared as described later. The residue from the second extract was a mixture of these acylamidothionaphthens. The aqueous liquor from the steam-distillation and the combined sodium carbonate washings gave on acidification 3-hydroxy-2-acetylcarbamyl-1-thionaphthen (III; R = Ac), which was synthesised as described later.

Reaction of 1-*chloroacetylbenz*isothiazolone. (i) At 70° for 1 hour. The solid which separated from the steam-distillate was 1-acetylbenz*iso*thiazolone; no other products were obtained.

(ii) At 95° for 25 minutes. The residue from the steam-distillation was filtered hot. The filtrate, on cooling, deposited 3-hydroxy-2-acetylcarbamyl-1-thionaphthen.

(iii) At 115° for 20 minutes. 3-Acetoxy-1-thionaphthen was not identified in the steam-distillate. Traces of an oil with similar properties were isolated. The residue from the steam-distillation was filtered hot. The filtrate, on cooling, deposited 3-acetamido-1-thionaphthen.

Reaction of 1-*phenylacetylbenz*isothiazolone. At 100° for 30 minutes. 3-Acetoxy-1-thionaphthen was not identified in the steam-distillate. Traces of an oil similar to that obtained in the previous experiment were obtained. After steam-distillation the aqueous solution was decanted from the oily material. Acidification of the solution gave 3-hydroxy-2-acetylcarbamyl-1-thionaphthen. The oily material was extracted with hot alcohol. The extract, on cooling, deposited 3-*phenylacetamido*-1-*thionaphthen*, which crystallised from alcohol in colourless prisms, m. p. 76° (Found: C, 71·8; H, 4·5. $C_{16}H_{13}ONS$ requires C, 71·9; H, 4·9%).

3-Phenylacetamido-1-thionaphthen (0·3 g.) in acetic acid (3 c.c.) and 2N-nitric acid (1 c.c.), heated for 10 minutes at 100°, gave a nitro-derivative, which crystallised from alcohol in yellow needles, m. p. 181°

Reaction of 2-*benzoylbenz*isothiazolone. At 105—110° for 20 minutes. The solid residue from the steam-distillation, fractionally crystallised from alcohol, gave 3-acetamido-1-thionaphthen and an impure material, from which 2-nitro-3-benzamido-1-thionaphthen was obtained by heating in acetic acid with 2N-nitric acid. Acidification of the residual liquid from the steam-distillation gave 3-hydroxy-2-acetylcarbamyl-1-thionaphthen.

*Reaction of benz*isothiazolone (4 g.). (i) At 110° for 30 minutes. The residue after steam-distillation, on cooling, deposited 3-acetamido-1-thionaphthen (1·5 g.), which was filtered off. The filtrate on acidification gave 3-hydroxy-2-acetylcarbamyl-1-thionaphthen (0·2 g.).

(ii) At 70° for 1½ hours. 3-Acetamido-1-thionaphthen (0·5 g.) and 3-hydroxy-2-acetylcarbamyl-1-thionaphthen (1·5 g.) were obtained.

(iii) At 50° for 1 hour. 1-Acetylbenz*iso*thiazolone only was obtained.

3-*Propionamido*-1-*thionaphthen* (II; R = $CO{\cdot}C_2H_5$).—3-Amino-1-thionaphthen (Fries and Hemmecke, *Annalen*, 1929, **470**, 1), heated with excess of propionic anhydride at 100°, gave 3-*propionamido*-1-*thionaphthen*, which crystallised from dilute propionic acid in colourless needles, m. p. 115° (Found: C, 64·1; H, 5·7. $C_{11}H_{11}ONS$ requires C, 64·4; H, 5·4%).

3-Propionamide-1-thionaphthen (0·2 g.) in acetic acid (1 c.c.) and 2N-nitric acid (0·5 c.c.) was heated at 100° for 15 minutes. The nitro-derivative which separated on cooling crystallised from aqueous alcohol in yellow needles, m. p. 171°.

2-*Bromo*-3-*propionamido*-1-*thionaphthen*.—Bromine (0·2 g.) in chloroform (6 c.c.) was added to a solution of 3-propionamido-1-thionaphthen (0·2 g.) in chloroform. Evaporation of the chloroform gave the required material, which crystallised from alcohol in white needles, m. p. 156° (Found: Br, 27·5. $C_{11}H_{10}ONBrS$ requires Br, 28·1%).

2-*Nitro*-3-*benzamido*-1-*thionaphthen*.—3-Benzamido-1-thionaphthen (0·5 g.) was heated with 2N-nitric acid (2 c.c.) in acetic acid for 5 minutes. The material precipitated by addition of water crystallised from alcohol in yellow needles, m. p. 180° (Found: C, 60·6; H, 3·9. $C_{15}H_{10}O_3N_2S$ requires C, 60·4; H, 3·4%).

2-*Carboxyphenylthiolacetamide* (IV).—Chloroacetamide (6·2 g.) was added to a solution of 2-thiolbenzoic acid (10 g.) in 2N-sodium hydroxide (65 c.c.). After 2 hours, the mixture was acidified; the precipitated material crystallised from alcohol in white needles, m. p. 210° (Found: C, 51·5; H, 4·2. $C_9H_9O_3NS$ requires C, 51·2; H, 4·3%).

3-Hydroxy-2-acetylcarbamyl-1-thionaphthen (III; R = Ac).—2-Carboxyphenylthiolacetamide (5 g.) was refluxed with acetic anhydride (10 c.c.) for 1 hour. Addition of water precipitated the required material, which crystallised from alcohol in white plates, m. p. 204° (Found: C, 56·1; H, 3·8; N, 5·7; S, 13·0. $C_{11}H_9O_3NS$ requires C, 56·1; H, 3·9; N, 6·0; S, 13·6%). It is soluble in aqueous sodium carbonate with a mauve fluorescence, gives a green coloration with alcoholic ferric chloride, and is readily oxidised to thioindigotin in alkaline solution by potassium ferricyanide.

3-Hydroxy-2-acetylcarbamyl-1-thionaphthen (1 g.) in acetic anhydride (0·5 c.c.) and toluene (10 c.c.) was refluxed for 1 hour. Addition of light petroleum precipitated *3-acetoxy-2-acetylcarbamyl-1-thionaphthen* (III; R = Ac, with OAc instead of OH), which crystallised from benzene–petroleum in white needles, m. p. 130° (Found: S, 11·7. $C_{13}H_{11}O_4NS$ requires S, 11·6%). It gives no coloration with alcoholic ferric chloride and is hydrolysed to 2-carbamyl-1-thionaphthen on standing in 2N-sodium hydroxide at room temperature for 2 hours.

3-Hydroxy-2-acetylcarbamyl-1-thionaphthen (1 g.), acetic anhydride (5 c.c.), and potassium acetate (1·2 g.), heated at 110° for 30 minutes, gave 3-hydroxy-2-acetyl-1-thionaphthen and 3-acetoxy-1-thionaphthen, which were isolated by steam-distillation in the usual way. The reaction was incomplete.

3-Hydroxy-2-carbamyl-1-thionaphthen (III; R = H).—A solution of 3-hydroxy-2-acetylcarbamyl-1-thionaphthen (1 g.) in 2N-sodium hydroxide (50 c.c.) was acidified after 24 hours. The precipitated material crystallised from alcohol in white needles, m. p. 208° (depression with starting material) (Found: N, 7·0. $C_9H_7O_2NS$ requires N, 7·2%). It gives a blue coloration with alcoholic ferric chloride and is oxidised to thioindigotin by alkaline potassium ferricyanide.

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