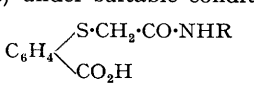
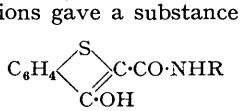
19. *The Formation of Thionaphthens from Derivatives of Phenylthioacetic Acid.*

By (the late) ERNEST W. MCCLELLAND, MAURICE J. ROSE, and DOUGLAS W. STAMMERS.

Condensation of either 2-carboxyphenylthioacetamide (I) or 2-carbamylphenylthioacetic acid (III; R = H) with potassium acetate and acetic anhydride yields the same 3-hydroxy-2-carbamylthionaphthen (II; R = H), the latter change involving a migration of the amino-group. It is shown that this transformation occurs through the cyclic *imide* (IV) which has been isolated and shown to yield the same products. A number of analogous compounds with alkyl or aryl groups substituted in the amino-group have been prepared and shown to behave in a similar manner. The mechanism of this reaction and that of the closely related condensation with benz*iso*thiazolones under similar conditions are discussed in detail.

2-CARBOXYPHENYLTHIOACETAMIDE (I; R = H) reacts normally with potassium acetate and acetic anhydride to give 3-hydroxy-2-carbamylthionaphthen (II; R = H) (compare McClelland, Rose, and Bartlett, *J.*, 1940, 323) but the isomeric amide (III; R = H) also gives this carbamylthionaphthen under similar conditions. The formation of carbamylthionaphthens equally from such isomeric amides appears to be general, for it has now been found that the *N*-substituted amides (I; R = Ph or CH_2Ph) and (III; R = Me, Et, CH_2Ph, or Ph) give the corresponding *N*-substituted carbamylthionaphthens. The conversion of amides of the type (I) into carbamylthionaphthens involves a simple dehydration but the conversion of the isomeric amides (III) involves a migration of the amino-group from one carbonyl group to the other. It seemed probable that this change occurs through the intermediate formation of a seven-membered ring compound (IV) produced by loss of water, and dehydration of the amide (III) under suitable conditions gave a substance which proved to be in fact an *imide* of the


(I.)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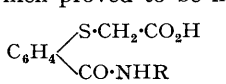
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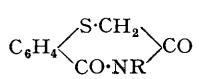
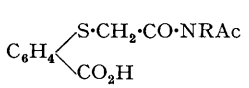

(IV.)

structure (IV; R = H). Thus, hydrolysis of the imide gives *o*-carboxyphenylthioacetic acid; it forms a potassium salt, which on treatment with alkyl halides gives the N-*alkylimides*

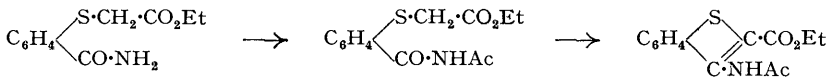
(IV; R = Me or Et). The N-*arylimides* (IV; R = CH_2Ph or Ph) on the other hand were obtained by dehydration of the corresponding amides (III; R = CH_2Ph, Ph).

The observation that the imide and its *N*-derivatives, when heated with potassium acetate and acetic anhydride, gave the corresponding hydroxycarbamylthionaphthens, supports the view that such seven-membered ring compounds are intermediates in the transformation observed. The change from the cyclic intermediate to the hydroxycarbamylthionaphthen may be conceived either as a direct change due to valency rearrangement with migration of one hydrogen atom, or through some intermediate compound produced by ring opening, such as (V).



(V.)

The formation of seven-membered ring compounds requires a free carboxyl group in the amide since the corresponding ester (ester of III) reacts normally with potassium acetate and acetic anhydride to give the aminothionapthen derivative (VI) and not a carbamylthionaphthen. It seems probable that the first stage in this reaction is acetylation of the amino-group, which by decreasing the basic properties of the nitrogen atom must enhance the reactivity of the carbonyl group. This will favour the internal condensation to the aminothionaphthen thus :

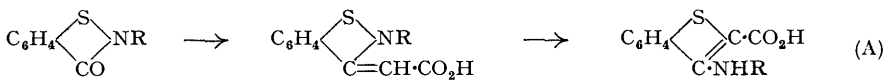


(VI.)

In addition to the hydroxycarbamylthionaphthen, 3-acetoxythionaphthen and 3-hydroxy-2-acetylthionaphthen were usually obtained in the reactions of the amides (I) and (III) with potassium acetate and acetic anhydride, referred to in the first paragraph above.

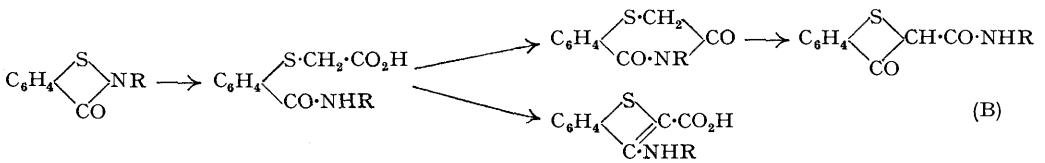
It has been shown (McClelland, *J.*, 1929, 1588; McClelland and D'Silva, *J.*, 1931, 2972) that benz*iso*thiazolones react with potassium acetate and acetic anhydride to give the hydroxyacetylthionaphthens and carbamylthionaphthens, and in the case of *N*-acylbenz*iso*thiazolones, aminothionaphthens. The latter have not been isolated where the *N*-substituent of the benz*iso*thiazolone is an alkyl or aryl group.

It was suggested (Bartlett and McClelland, *J.*, 1934, 818) that thionaphthens were formed from benz*iso*thiazolones by the following steps :



(A)

but this does not explain the production of carbamylthionaphthens which had not at that time been detected as products. The similarity in the products of the reaction of amides of type (III) and of benz*iso*thiazolones with potassium acetate and acetic anhydride suggests that the amide is an intermediate in the reaction of a benz*iso*thiazolone. It seems probable, therefore, that the first stage in the reaction of a benz*iso*thiazolone with potassium acetate and acetic anhydride is ring fission to give amides of this type, which react in the manner described to give the seven-membered ring and hence hydroxycarbamylthionaphthens thus :



(B)

The formation of acylamidothionaphthens when *N*-acylbenz*iso*thiazolones react with potassium acetate and acetic anhydride may be due to the reaction proceeding in part by mechanism (A), or alternatively that the *N*-acylamide produced by ring fission of the benz*iso*thiazolone yields the aminothionaphthen by internal condensation. The acetyl group of the amide should enhance the reactivity of the carbonyl group in either (A) or (B) and thus promote this process. The absence of the aminothionaphthen type of compound in the reaction products from *N*-aryl- or -alkyl-benz*iso*thiazolones can be attributed to the lower reactivity of the carbonyl group preventing the formation of the aminothionaphthen. The *N*-alkyl- or -aryl-amides therefore tend to give the seven-membered ring intermediate and yield hydroxycarbamylthionaphthens to the exclusion of aminothionaphthens.

It has been previously shown that hydroxycarbamylthionaphthen itself reacts with

potassium acetate and acetic anhydride to give 3-hydroxy-2-acetylthionaphthen and 3-acetoxythionaphthen.

The suggestion also made previously (McClelland and Bartlett, *loc. cit.*), that direct carbon-acetylation might be involved in the formation of 3-hydroxy-2-acetylthionaphthen, has now been subjected to a rigorous experimental test. It was found that 3-hydroxy-2-propionylcarbamylthionaphthen, heated with propionic anhydride and sodium propionate, yielded in the same way a mixture of 3-hydroxy-2-propionylthionaphthen and 3-propoxythionaphthen, yet carefully purified 3-propoxythionaphthen heated under similar conditions did not give any of the 2-propionyl derivative. The idea that direct carbon-acylation takes place is therefore negatived.

Hence all the products so far detected in the reaction of various benz*iso*thiazolones are accounted for. Some related experiments with 2-cyanophenylthioacetic acid, in which various metoxazine derivatives were produced, are described in the preceding paper.

Experimental.

Reactions of 2-Carboxyphenylthioacetamides with Potassium Acetate and Acetic Anhydride.—(1) 2-Carboxyphenylthioacetamide (McClelland, Rose, and Bartlett, *loc. cit.*) (3 g.), heated with freshly fused potassium acetate (3·7 g.) and acetic anhydride (16 c.c.) at 110° for ½ hour, yielded the steam-volatile products 3-acetoxy- and 3-hydroxy-2-acetylthionaphthen together with 3-hydroxy-2-acetylcarbamylthionaphthen.

(2) When this reaction was repeated but with sodium propionate and propionic anhydride and the products were distilled in steam, the residual solution on acidification gave *3-hydroxy-2-propionylcarbamylthionaphthen*, crystallising from alcohol in white needles, m. p. 188° (Found: C, 57·9; H, 4·4. $C_{12}H_{11}O_3NS$ requires C, 57·8; H, 4·4%). The substance gives a green-blue colour with ferric chloride and is readily oxidised by alkaline ferricyanide to thioindigo. Acetylation with acetic anhydride in boiling toluene yielded the O-*acetyl* derivative, crystallising from ether in long fibrous needles, m. p. 80° (Found: C, 57·7; H, 4·5. $C_{14}H_{13}O_4NS$ requires C, 57·7; H, 4·5%).

The products which distilled in steam were extracted with aqueous sodium hydroxide, the alkaline solution depositing on acidification 3-hydroxy-2-propionylthionaphthen, m. p. 73° (Krollpfeifer and Schneider, *Ber.*, 1928, **61**, 1284). The insoluble portion was recovered as a red oil identified as 3-propoxythionaphthen. It gave no colour with ferric chloride and was readily oxidised to thioindigo by ferricyanide; heated with aniline at 100° for 1 hour, it yielded propanilide, m. p. 103°, and heated with phenylhydrazine for 1 hour at 100°, furnished thionaphthindole, m. p. 253°.

When 2-carboxyphenylthioacetamide was heated with propionic anhydride alone at 140° for 1 hour the same 3-hydroxy-2-propionylcarbamylthionaphthen was the sole product. This substance, heated with sodium propionate and propionic anhydride at 140° for 2 hours, gave 3-hydroxy-2-propionylthionaphthen and 3-propoxythionapthen. The latter, carefully purified by washing its ethereal solution with alkali and water, the solution being then dried and evaporated, was heated with sodium propionate and propionic anhydride at 140° for 3 hours. No trace of 3-hydroxy-2-propionylthionaphthen could be detected in the resulting mixture.

(3) *o*-Mercaptobenzoic acid (4·5 g.) in aqueous sodium hydroxide (2·3 g.) was heated for ¼ hour on the water-bath with ω-chloroacetanilide (5 g.), and the product precipitated by acidification. *2-Carboxyphenylthioacetanilide* was thus isolated (yield 90%), crystallising from alcohol in white needles, m. p. 220° (Found: C, 63·1; H, 4·3; N, 4·8. $C_{15}H_{13}O_3NS$ requires C, 62·7; H, 4·5; N, 4·9%). This acid was unaffected by heating in boiling toluene with phosphoric oxide. Heated with acetic anhydride, it yielded only 2-bis-(3-acetoxythionaphthen), m. p. 166°.

When *o*-carboxyphenylthioacetanilide was heated at 110° for ½ hour with acetic anhydride and potassium acetate the products volatile in steam were 3-hydroxy-2-acetyl- and 3-acetoxy-thionaphthen, the residue being 3-hydroxy-2-phenylcarbamylthionaphthen, m. p. 235° (Bartlett and McClelland, *loc. cit.*).

(4) Condensation of *o*-mercaptobenzoic acid with ω-chloroacetbenzylamide (Jacobs and Heidelberger, *J. Biol. Chem.*, 1915, **20**, 685) gave *2-carboxyphenylthioacetbenzylamide*, crystallising from alcohol in needles, m. p. 186° (Found: C, 64·0; H, 4·9. $C_{16}H_{15}O_3NS$ requires C, 63·8; H, 5·0%). When this substance was heated for ½ hour at 130° with acetic anhydride and potassium acetate the products were 3-hydroxy-2-acetyl-, 3-acetoxy- and 3-hydroxy-2-benzylcarbamyl-thionaphthen (m. p. 132°; Bartlett and McClelland, *loc. cit.*).

(5) Condensation of *o*-mercaptobenzoic acid with ω-chloroacetylbenzamide (Abderhalden and Reisz, *Fermentforschung*, 1930, **12**, 180—222, furnished *2-carboxyphenylthioacetylbenzamide*, crystallising from dioxan in small needles, m. p. 224° (Found: C, 61·2; H, 4·2. $C_{16}H_{13}O_4NS$ requires C, 61·0; H, 4·1%). This compound, when heated at 110° for ¼ hour with potassium acetate and acetic anhydride, yielded 3-hydroxy-2-acetyl-, 3-acetoxy-, and (not volatile in steam) 3-hydroxy-2-acetylcarbamyl-thionaphthen (m. p. 204°).

Reactions of 2-Carbamylphenylthioacetic Acids and Their Derivatives with Potassium Acetate and Acetic Anhydride.—(1) *2-Carbamylphenylthioacetic acid* was prepared from *o*-mercaptobenzamide (compare D.R.-P. 570,364) (yield 73%). It formed colourless needles, m. p. 207°, from water (Found: N, 6·6. $C_9H_9O_3NS$ requires 6·6%). Oxidation in 2N-acetic acid with hydrogen peroxide (5 c.c. of 90-vol. per g.) at 100° yielded *2-carbamylphenylsulphinylacetic acid*, colourless needles, m. p. 210° (Found: C, 47·4; H, 4·3. $C_9H_9O_4NS$ requires C, 47·6; H, 4·0%). With hydrogen peroxide (90-vol., 2·5 c.c. per g.) in glacial acetic acid at 100° the sulphone was produced. By successive crystallisation from hot water and methanol, *2-carbamylphenylsulphonylacetic acid* was obtained in needles, m. p. 176—178° (Found: C, 44·4; H, 3·5; N, 5·5. $C_9H_9O_5NS$ requires C, 44·4; H, 3·7; N, 5·8%). This substance separates

from water in colourless prisms, m. p. *ca.* 137°, of the *monohydrate* (Found : H_2O, 7·0. $C_9H_9O_5NS,H_2O$ requires H_2O, 6·9%).

When 2-carbamylphenylthioacetic acid was heated for ½ hour at 105° with potassium acetate and acetic anhydride the products identified were 3-hydroxy-2-acetyl-, 3-acetoxy-, and 3-hydroxy-2-acetylcarbamyl-thionaphthen.

The corresponding *ethyl 2-carbamylphenylthioacetate*, obtained from 2-mercaptobenzamide and ethyl chloroacetate, forms colourless needles from hot water, m. p. 97° (Found : C, 55·1; H, 5·4; S, 13·3. $C_{11}H_{13}O_3NS$ requires C, 55·2; H, 5·4; S, 13·4%). When this ester was heated with potassium acetate and acetic anhydride at 145—150° for ½ hour, no steam-volatile products were found. The main product was *ethyl 3-acetoxythionaphthen-2-carboxylate*, m. p. 105°, identical with that obtained by acetylation of 3-hydroxythionaphthen-2-carboxylate (Found : C, 58·8; H, 4·3; S, 12·0. $C_{13}H_{12}O_4S$ requires C, 59·1; H, 4·5; S, 12·1%). It is insoluble in acid or alkali, gives no ferric chloride reaction, is not oxidised to thioindigo by ferricyanide, and yields on heating with aniline ethyl 3-hydroxythionaphthen-2-carboxylate, m. p. 74°, and acetanilide. In addition, the main condensation yielded a little ethyl hydroxythionaphthencarboxylate and a yellow oil which proved to be ethyl 3-acetamidothionapthen-2-carboxylate, hydrolysed to 3-amino-2-carboxythionaphthen (see *Annalen*, 1907, **351**, 416). This substance gave with acetic anhydride, or in benzene solution with acetyl chloride, the N-*acetyl* derivative, crystallising from glacial acetic acid in colourless needles, m. p. 230° (Found : C, 56·2; H, 3·7. $C_{11}H_9O_3NS$ requires C, 56·2; H, 3·8%), and unchanged by heating with acetic anhydride and potassium acetate. The identity of the aminocarboxythionaphthen was also confirmed by its conversion into 3-hydroxythionaphthen on distillation with dilute sulphuric acid.

When ethyl carbamylphenylthioacetate was heated with acetic anhydride alone at 140—145° for ½ hour, ethyl 3-hydroxythionaphthen-2-carboxylate and ethyl 3-acetamidothionaphthen were again obtained.

2-Carbamylphenylthioacetic acid (10 g.) was boiled with acetic anhydride (15 c.c.) in toluene (100 c.c.) until solution was complete (3—5 hours). Light petroleum (200 c.c.) was added to the cold solution, and the mixture left for 24 hours. The product which separated was the cyclic *imide*, which formed colourless needles from dilute acetic acid, m. p. 143° (yield 60%) (Found : C, 55·9; H, 3·6; N, 7·2; *M*, ebullioscopic in benzene, 197. $C_9H_7O_2NS$ requires C, 56·0; H, 3·6; N, 7·3%; *M*, 193). The same product was obtained by heating with propionic anhydride at 100°.

The imide is soluble in organic solvents and in hot aqueous acetic acid. It dissolves in cold aqueous sodium hydroxide and is reprecipitated on acidification, but it is not dissolved by aqueous ammonia or sodium hydrogen carbonate. It gave no colouration with ferric chloride or alkaline potassium ferricyanide. Heated in boiling water for 6 hours, it was hydrolysed to the parent carbamylphenylthioacetic acid. It was unaffected by boiling aniline, by *p*-toluenesulphonyl chloride in hot pyridine, by diazomethane in ether, and by nitrous acid. Warmed with resorcinol and sulphuric acid, it yields an orange solution which, on dilution and being made alkaline, shows a green fluorescence.

The formation of this imide could not be detected when 2-carboxyphenylthioacetamide was heated at 110° with acetic anhydride for 1 hour or for shorter times, the only product found being 3-hydroxy-2-acetylcarbamylthionaphthen, m. p. 203°.

When the imide was heated at 110° for 20 minutes with potassium acetate and acetic anhydride it reacted vigorously to produce 3-hydroxy-2-acetyl-, 3-acetoxy-, and 3-hydroxy-2-acetylcarbamyl-thionaphthen.

Addition of alcoholic potassium ethoxide to a solution of the imide in dioxan yielded the *potassium* salt as a microcrystalline powder which was washed with alcohol and benzene and dried in a vacuum (Found : K, 16·7. $C_9H_6O_2NSK$ requires K, 16·9%). Heated in a sealed tube at 100° for 3 hours with methyl iodide (3 mols.), it gave the N-*methylimide*, crystallising from alcohol in colourless needles, m. p. 97° (yield 56%) (Found : C, 58·1; H, 4·4. $C_{10}H_9O_2NS$ requires C, 58·0; H, 4·3%). This substance is insoluble in cold dilute alkali, but is hydrolysed on boiling to 2-methylcarbamylphenylthioacetic acid, m. p. 146°. It gives no colour with ferric chloride or alkaline ferricyanide.

Heated at 100° for 6 hours with potassium acetate and acetic anhydride, the *N*-methylimide gave a mixture, containing no steam-volatile thionaphthens, from which, by extraction with aqueous ammonium carbonate and acidification of the solution, 3-hydroxy-2-methylcarbamylthionaphthen, m. p. 123° (Bartlett and McClelland, *loc. cit.*) was isolated, which gave the characteristic reactions of this substance.

The N-*ethylimide*, from the potassium salt and ethyl bromide in a sealed tube, crystallised from aqueous alcohol (charcoal) in colourless prisms, m. p. 72° (yield, 42%) (Found : C, 59·9; H, 4·9. $C_{11}H_{11}O_2NS$ requires C, 59·7; H, 5·0%).

(2) 2 : 2′-Dithiobenzomethylamide (10 g.) was reduced with zinc dust (10 g.) and alcoholic hydrochloric acid in a current of nitrogen, and the filtered solution evaporated under reduced pressure. The solid product was condensed with sodium chloroacetate (8 g.) in aqueous sodium hydroxide (125 c.c., 2N) at 100° for ½ hour. Acidification gave a precipitate of 2-*methylcarbamylphenylthioacetic acid*, colourless needles, m. p. 146°, from alcohol (Found : C, 53·4; H, 5·3. $C_{10}H_{11}O_3NS$ requires C, 53·3; H, 4·9%). Heated with potassium acetate and acetic anhydride at 100° for 6 hours, it yielded 3-acetoxythionaphthen and a trace of 3-hydroxy-2-acetylthionaphthen.

(3) From 2 : 2′-dithiobenzoethylamide was obtained 2-*ethylcarbamylphenylthioacetic acid* (yield, 65%) as colourless prisms, m. p. 125°, from aqueous acetic acid (Found : C, 55·4; H, 5·6. $C_{11}H_{13}O_3NS$ requires C, 55·2; H, 5·4%). Heated at 100° for 3 hours with potassium acetate and acetic anhydride, it yielded 3-acetoxy-1-thionaphthen, 2-bis-(3-acetoxythionaphthen), m. p. 166°, and by extraction with ammonium carbonate and acidification, 3-hydroxy-2-ethylcarbamylthionaphthen of m. p. 133° and showing the characteristic reactions of this substance (Bartlett and McClelland, *loc. cit.*).

(4) 2-*Benzylcarbamylphenylthioacetic acid*, obtained from 2 : 2′-dithiobenzobenzylamide (yield, 72%), forms colourless needles, m. p. 142°, from aqueous acetic acid (Found : C, 63·9; H, 5·1. $C_{16}H_{15}O_3NS$ requires C, 63·8; H, 5·0%). This acid was heated at 100° for 4 hours with acetic anhydride (2 parts) and potassium acetate (½ part), the mixture poured into water, and 3-acetoxythionaphthen removed in a current of steam. The residual brown oil was washed with water, boiled with 50% acetic acid, and the

solution evaporated under diminished pressure. The material was dissolved in ether and extracted with aqueous N-sodium hydroxide. The alkaline solution furnished unchanged 2-benzylcarbamylphenylthioacetic acid and 3-hydroxy-2-benzylcarbamylthionaphthen. The ethereal solution was washed successively with dilute acid and water, dried over sodium sulphate, and evaporated. The viscous brown oil remaining was further purified by charcoal in 90% alcohol, the solution evaporated at 100°, and the oil dried in a vacuum for 3 days. The N-*benzylimide* was thus obtained as an oil which could not be distilled under diminished pressure (Found: C, 62·7; H, 4·8; S, 11·2. $C_{16}H_{13}O_2NS$ requires C, 67·8; H, 4·6; S, 11·3%). It was hydrolysed to the parent acid by standing for 3 days with cold alcoholic 5% sodium hydroxide.

When the benzylcarbamylphenylthioacetic acid was heated with potassium acetate and acetic anhydride at 100° for 9 hours the products isolated were 3-acetoxythionaphthen and 3-hydroxy-2-benzylcarbamylthionaphthen, m. p. 130°. The *N*-benzylimide with the same reagents under similar conditions furnished the same products.

A separate experiment showed that the acid was recovered unchanged after standing for 3 days in alcholic sodium hydroxide solution.

(5) 2-*Phenylcarbamylphenylthioacetic acid*, obtained from 2 : 2′-dithiobenzanilide (yield, 73%), crystallised from aqueous alcohol in white plates, m. p. 137° (Found: C, 63·0; H, 4·6. $C_{15}H_{13}O_3NS$ requires C, 62·7; H, 4·5%). Heated with potassium acetate and acetic anhydride at 110—115° for 20 minutes, it yielded 3-hydroxy-2-acetyl-, 3-acetoxy-, and 3-hydroxy-2-phenylcarbamyl-thionaphthen (Bartlett and McClelland *loc. cit.*).

The acid (1 part) was heated at 100° for 5 hours with acetic anhydride (2 parts), and excess of the latter removed by three extractions with light petroleum. The residual oil was purified by solution in toluene and precipitation with light petroleum, followed by the action of charcoal in alcoholic solution, and finally it was recovered and kept in a vacuum for 2 days. The N-*phenylimide* was thus obtained as an oil which could not be distilled (Found: S, 11·6. $C_{15}H_{11}O_2NS$ requires S, 11·9%). It was not immediately soluble in dilute alkali but dissolved on standing for 15 minutes and the solution on acidification deposited the parent acid once more. Heated at 100° for 1 hour with potassium acetate and acetic anhydride, it gave the same three substances as were obtained from the acid under similar conditions.

3-Hydroxy-2-phenylcarbamylthionaphthen was also heated with potassium acetate and acetic anhydride for ½ hours at 110°. 3-Hydroxy-2-acetyl- and 3-acetoxy-thionaphthen were removed in a current of steam, and the residue yielded mainly N-*acetylphenylcarbamyl*-3-*acetoxythionaphthen*, white plates from alcohol, m. p. 138° (Found: S, 8·7. $C_{19}H_{15}O_4NS$ requires S, 9·1%). It yielded on alkaline hydrolysis 3-hydroxy-2-phenylcarbamylthionaphthen, and the latter was also present in the mother-liquors of the preparation. A little 3-hydroxy-1-thionaphthen was also formed.

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