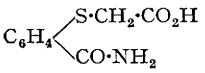
18. *Some* 1 : 3-*Oxazine Derivatives of Thionaphthen.*

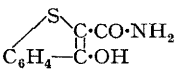
By (the late) Ernest W. McClelland and Douglas W. Stammers.

2-Cyanophenylthioacetic acid (IV) condenses with acetic anhydride and potassium acetate, the principal product being 3-acetamido-2-carboxythionaphthen (VI), but yellow by-products (XII) and (XVII) are also formed which are metoxazine derivatives of complexity varying with the conditions of the reaction. Their structures are discussed, and it is also shown that the acetamidocarboxythionaphthen is converted directly by hot acetic anhydride into a thionaphtheno-1 : 3-oxazine (VII) which reacts with ammonia to give the corresponding thionaphthenopyrimidine (VIII).

In the course of a study of the formation of thionaphthens by condensation of 2-substituted phenylthioacetic acids with acetic anhydride and potassium acetate several thionaphtheno-1 : 3-oxazines have been encountered.

It has been shown (McClelland, Rose, and Stammers, following paper) that 2-carbamylphenylthioacetic acid (I) is converted by acetic anhydride and potassium acetate into the carbamylthionaphthen (II) and that the imide (III) is an intermediate in the process. If, in the


(I.)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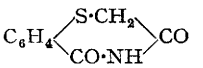
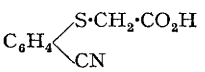

(III.)

similar condensation with the 2-cyano-acid (IV), the first step was an internal self-addition the same imide would result and the carbamidothionaphthen would be the final product.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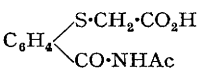
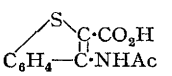
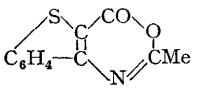

(V.)

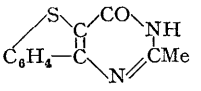

(VI.)

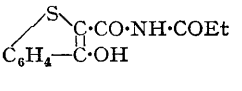
Alternatively, however, addition of acetic acid to the cyano-group might occur to give the 2-acetylcarbamyl acid (V) and this would undergo internal condensation to produce 3-acetamido-

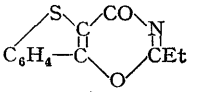
2-carboxythionaphthen (VI). The condensation proceeded, in fact, according to the second of these schemes and the acetamidocarboxythionaphthen was the principal product, but it was accompanied, according to the conditions used, by two yellow *by-products*, A and B, which are discussed below.

The formation of a 1 : 3-oxazine ring was to be expected from substances containing the grouping of (VI), analogous cases being the production of 1 : 3-oxazines from *N*-benzoylanthranilic acid (Shroeter, *Ber.*, 1920, **53**, 230) and α-benzamidocinnamic acid (Erlenmeyer, *Annalen*, 1893, **275**, 1), and experiment showed that this acetamidocarboxythionaphthen is converted by hot acetic anhydride into 6-*keto*-2-*methylthionaphtheno*(3′ : 2′ : 4 : 5)-1 : 3-*oxazine* (VII), which reacted readily with ammonia to give the corresponding *thionaphthenopyrimidine* (VIII) (compare the formation of *iso*carbostyril from *iso*coumarin, Bamberger and Frew, *Ber.*,


(VII.)

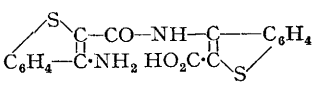

(VIII.)

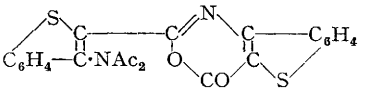

(IX.)

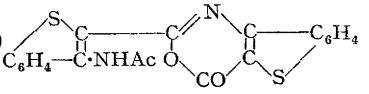

(X.)

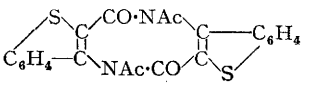
1894, **27**, 208; Gabriel and Neumann, *Ber.*, 1892, **25**, 3563). 3-Hydroxy-2-propionylcarbamylthionaphthen (IX) was similarly converted by hot propionic or acetic anhydride into 4-*keto*-2-*ethylthionaphtheno*(2′ : 3′ : 5 : 6)-1 : 3-*oxazine* (X).

Of the yellow by-products, referred to above, B was obtained when the reaction was conducted at 140—145°. It was of high melting point, was insoluble in alkali, and had a composition which may be expressed in the form (cyano-acid + $CO{\cdot}CH_2$ — $H_2O)_x$, but it was too sparingly soluble in organic solvents or molten camphor for the determination of molecular weight. It was hydrolysed by alcoholic alkali to give sodium acetate and a *substance* C of the composition (cyano-acid — $H_2O)_x$. C was soluble in aqueous bicarbonate, and hot acetic anhydride reconverted it into B. If it is assumed, therefore, that $x = 2$, the substance C might be the amide of structure (XI) and B might be the *N*-diacetyl derivative of a thionaphtheno-1 : 3-oxazine (XII) or the diacetyl derivative of a cyclic diamide such as (XIII). Of these two, structure (XII) requires that the two acetyl groups should differ in ease of hydrolysis.

(XI.) (C.) 

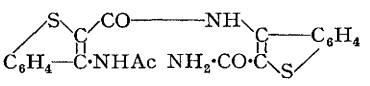

(XII.) (B.)

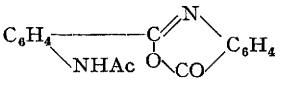
(XII*a*.) (D.) 

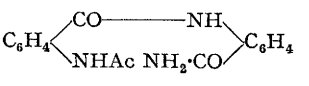

(XIII.)

It was found, in fact, that B readily lost one acetyl group on boiling with 90% acetic acid, yielding a *compound* D which was reconverted into B by acetic anhydride and hydrolysed by alkali to C; B therefore has structure (XII) and D the structure (XII*a*) with NHAc in place of NAc_2. The conclusion was further confirmed by the conversion of D by propionic anhydride into the corresponding N-*acetyl*-N′-*propionyl* compound and of C in a similar manner into its *mono*- and *di*-N-*propionyl* derivatives analogous to D and B respectively.

When B was subjected to the action of ammonia in alcoholic solution no pyrimidine was isolated, but instead 3-*acetamido*-2-(2′-*carbamyl*-3′-*thionaphthenyl*)*carbamylthionaphthen* (XIV) resulted, the metoxazine ring having been opened [compare the action of ammonia on the acetamidophenylbenz-1 : 3-oxazine (XV) to give acetylanthranoylanthranilic acid amide (XVI); Mohr and Kohler, *Ber.*, 1907, **40**, 997].


(XIV.)

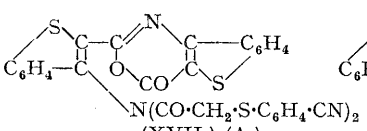

(XV.)


(XVI.)

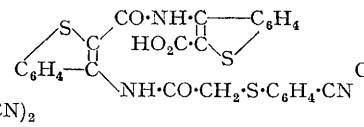
When the condensation with cyanophenylthioacetic acid was carried out at a lower temperature (100°), another by-product A was produced which was highly insoluble and of the composition (cyano-acid — $H_2O)_m$. It was acted upon by hot acetic anhydride to produce B (XII) together with some of the acetamidocarboxythionaphthen. Vigorous hydrolysis of A yielded C (XI) without the formation of any sodium acetate. Hydrolysis under milder conditions gave 3-amino-2-carboxythionaphthen and a new highly insoluble *substance* L of a

composition represented by (3 cyano-acid — $2H_2O$). L, boiled with either acetic or propionic anhydride, was converted into a *substance* M with the composition (cyano-acid — $H_2O)_n$ which was reconverted into L by cold alcoholic alkali; M thus had the same empirical composition as A but was quite distinct from it. Friedländer and Laske's observation (*Annalen*, **1907**, **351**, 416) that the 2-cyanophenylthioacetic acid is itself converted on standing with cold alcoholic alkali into 3-amino-2-carboxythionaphthen was confirmed.

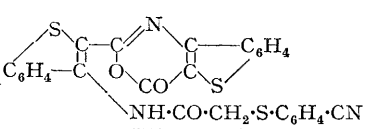
Bearing in mind that the presence of the cyano-acid appears to be a condition of the formation of the yellow by-products, the facts above summarised lead to the supposition that $m = 4$ and $n = 3$ in the above expressions and that A has the structure (XVII). Its conversion into B (XII) by acetic anhydride is then a simple displacement of cyanophenylthioacetyl radicals by acetyl radicals. L will therefore be the substance (XVIII) closely related to (XIV) and M must have the 1 : 3-oxazine structure (XIX) analogous to D.



(XVII.) (A.)



(XVIII.) (L.)



(XIX.) (M.)

Experimental.

Condensation of 2-Cyanophenylthioacetic Acid with Acetic Anhydride and Potassium Acetate.—(1) 2-Cyanophenylthioacetic acid (10 g.; cf. Friedländer and Laske, *loc. cit.*, p. 413; D.R.-P. 184,496) was heated for ½ hour at 140—145° with acetic anhydride (30 c.c.) and potassium acetate (7·5 g.). The solid deposited on cooling was washed with acetic anhydride and with water and heated for ½ hour at 100° with acetic acid (100 c.c.; 80%). The solid product was separated when cold and extracted with aqueous sodium hydroxide (30 c.c.; 2N) at 60° for ½ hour. The alkaline solution on acidification yielded 3-acetamido-2-carboxythionaphthen, m. p. 230° (yield, 6·4 g.).

The residue insoluble in alkali (compound B) formed yellow prisms, m. p. 259°, from acetic anhydride (yield 0·9 g.). This was 3-*diacetylamino*-2-6′-*ketothionaphtheno*(3″ : 2″ : 4′ : 5′)-1 : 3-*oxazinyl*-2′-*thionaphthen* (XII) (Found : C, 60·7; H, 3·4; S, 14·9. $C_{22}H_{14}O_4N_2S_2$ requires C, 60·8; H, 3·2; S, 14·7%). It gave no coloration with ferric chloride or alkaline ferricyanide.

When heated in 90% acetic acid this substance suffered partial hydrolysis, and yellow needles of the *monoacetyl* compound D (XII*a*), m. p. 312°, separated, which were washed with hot alcohol and dried at 100° (Found : C, 61·4; H, 3·3; S, 16·2. $C_{20}H_{12}O_3N_2S_2$ requires C, 61·2; H, 3·1; S, 16·3%). This substance is insoluble in alkali and gives no colour with ferric chloride or alkaline ferricyanide. It is reconverted into compound B by heating with acetic anhydride, and with propionic anhydride yields the corresponding N-*acetyl*-N′-*propionyl* derivative, crystallising from propionic anhydride in yellow plates, m. p. 230° (Found : C, 61·7; H, 3·9. $C_{23}H_{16}O_4N_2S_2$ requires C, 61·6; H, 3·6%).

When B (XII) was heated in boiling alcohol for 1½ hours with a stream of ammonia passing, a small amount of compound D (XII*a*) was deposited early in the operation and was removed. The final solution on evaporation to dryness yielded 3-*acetamido*-2-(2′-*carbamyl*-3′-*thionaphthenyl*)*carbamylthionaphthen* (XIV) as a pale yellow microcrystalline powder of m. p. 284—286° (Found : C, 58·9; H, 3·9; N, 10·2. $C_{20}H_{15}O_3N_3S_2$ requires C, 58·7; H, 3·7; N, 10·3%).

When either D (XII*a*) or B (XII) was hydrolysed by alcoholic sodium hydroxide (10 parts; 5%) and the solution acidified at 70°, a solid was obtained which crystallised from glacial acetic acid in yellow needles, m. p. 246°, and was 3-*amino*-2-(2′-*carboxy*-3′-*thionaphthenyl*)*carbamylthionaphthen*, compound C (XI) (Found : C, 58·7; H, 3·5; S, 17·4. $C_{18}H_{12}O_3N_2S_2$ requires C, 58·7; H, 3·3; S, 17·4%). The aqueous mother-liquor from this hydrolysis contained sodium acetate and on distillation in steam yielded some 3-hydroxythionaphthen. C (XI) dissolved in aqueous sodium hydrogen carbonate with evolution of carbon dioxide. It gave no colouration with ferric chloride or alkaline ferricyanide. Heated with acetic anhydride it was reconverted into B (XII). Heated with propionic anhydride at 100° for ½ hour it yielded the N-*propionyl* derivative as yellow needles, m. p. 296°, from propionic anhydride (Found : C, 62·2; H, 3·2. $C_{21}H_{14}O_3N_2S_2$ requires C, 62·1; H, 3·4%). When heating was continued for a further ½ hour until all solid dissolved, the NN′-*dipropionyl* derivative separated on cooling in yellow prisms, m. p. 246° (Found : C, 62·2; H, 4·1. $C_{24}H_{18}O_4N_2S_2$ requires C, 62·3; H, 3·9%). Boiled for 1 hour with 90% propionic acid, this compound suffered partial hydrolysis to the preceding *N*-propionyl derivative.

(2) When 2-cyanophenylthioacetic acid was heated with acetic anhydride and potassium acetate at 100° for 40 minutes and the products were treated as before, the alkali-insoluble product was again 3-acetamido-2-carboxythionaphthen (yield 5 g.), but the residue was a bright yellow solid separating as a microcrystalline powder, m. p. 277—279°, from nitrobenzene (yield 0·8 g.). This compound A (XVII) was 3-(*bis*-o-*cyanophenylthioacetyl*)*amino*-2-6′-*ketothionaphtheno*(2″ : 3″ : 5′ : 4′)-1 : 3-*oxazinyl*-2′-*thionaphthen* (Found : C, 61·5; H, 2·8; N, 7·9. $C_{36}H_{20}O_4N_4S_4$ requires C, 61·7; H, 2·9; N, 8·0%). It was sparingly soluble in all organic solvents and unaffected by boiling in 80% acetic acid for 6 hours. When it was heated at 145° for 3 hours with acetic anhydride it yielded 3-acetamido-2-carboxythionaphthen and compound B. On hydrolysis with alcoholic sodium hydroxide (15%) for 4 hours it gave the yellow compound C (XI) of m. p. 246° and the mother-liquor was found not to contain sodium acetate.

A (XVII) was partly hydrolysed by standing for 24 hours with 5% aqueous alcoholic sodium hydroxide with occasional shaking. The solution was evaporated, the residue dissolved in water, and the solution

acidified at 70° with acetic acid. The precipitate was collected, washed, and dried in a vacuum and extracted with boiling light petroleum, evaporation of which yielded a trace of 3-amino-2-carboxythionaphthen. The residue was further purified by boiling with acetic acid and crystallised from nitrobenzene as a pale yellow microcrystalline powder, m. p. 260°. This was L (XVIII), 3-o-*cyanophenylthioacetamido*-2-(2′-*carboxy*-3′-*thionaphthenylcarbamyl*)*thionaphthen* (Found : C, 59·6; H, 3·4. $C_{27}H_{17}O_4N_3S_3$ requires C, 59·7; H, 3·1%). It was sparingly soluble in organic solvents but soluble in aqueous alkali. It gave no colouration with ferric chloride or alkaline ferricyanide. Heated for a few minutes with boiling acetic or propionic anhydride it yielded the alkali-insoluble M (XIX), 3-o-*cyanophenylthioacetamido*-2-6′-*ketothionaphtheno*(2″ : 3″ : 5 : 4)-1 : 3-*oxazinyl*-2′-*thionaphthen* as orange needles which could not be recrystallised. It was best obtained pure by preparing it from purified material and finally boiling the product successively with acetic acid and absolute alcohol (Found : C, 61·5; H, 3·2; S, 18·3. $C_{27}H_{15}O_3N_3S_3$ requires C, 61·7; H, 2·9; S, 18·0%). It was reconverted into its parent compound by standing in alcoholic alkali followed by acidification.

Metoxazines from Substituted Thionaphthens.—3-Acetamido-2-carboxythionaphthen was heated with acetic anhydride (4 parts) at 145° for ½ hour. The mixture yielded, on cooling, 6-*keto*-2-*methylthionaphtheno*(3′ : 2′ : 4 : 5)-1 : 3-*oxazine* (VII) as colourless needles, m. p. 179° (Found : C, 60·7; H, 3·4; S, 14·8. $C_{11}H_7O_2NS$ requires C, 60·8; H, 3·2; S, 14·7%). It was insoluble in alkali, gave a bright yellow colour with ferric chloride, and was hydrolysed to the parent substance by boiling for 20 minutes with 80% acetic acid. Heated at 40° for 20 minutes with alcoholic ammonia [30 c.c. of ethanol and 80 c.c. of ammonia (*d* 0·88) per g.] and then for a further 1 hour at 60°, it furnished 4-*keto*-2-*methyl*-3 : 4-*dihydrothionaphtheno*(2′ : 3′ : 5 : 6)*pyrimidine* (VIII) which crystallised in colourless needles, m. p. 340—345° (decomp.), from acetic acid (Found : C, 60·9; H, 3·9; N, 13·1. $C_{11}H_8ON_2S$ requires C, 61·1; H, 3·7; N, 13·0%). This substance dissolved in dilute alkali and was reprecipitated unchanged on acidification. It gave no colour with ferric chloride or alkaline ferricyanide.

3-Hydroxy-2-propionylcarbamylthionaphthen (McClelland, Rose, and Stammers, *loc. cit.*), heated at 130° for ½ hour with propionic anhydride or acetic anhydride, gave 4-*keto*-2-*ethylthionaphtheno*-(2′ : 3′ : 5 : 6)-1 : 3-*oxazine* (X) as colourless plates of m. p. 209° (Found : C, 62·2; H, 4·0. $C_{12}H_9O_2NS$ requires C, 62·3; H, 3·9%). It was reconverted into the parent substance by boiling with dilute acetic acid. It was insoluble in alkali, and gave no immediate colour with ferric chloride but a green colouration on warming.

The corresponding 3-hydroxy-2-acetylcarbamylthionaphthen under similar conditions yielded only the acetyl derivative of m. p. 130°.

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