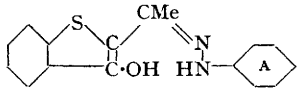
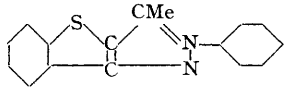
101. *An "Ortho-effect" in the Formation of Thionaphthenopyrazoles.*

By (the late) ERNEST W. MCCLELLAND and PHILIP W. SMITH.

It is shown that the conversion of phenylhydrazones of 3-hydroxy-2-acetyl-1-thionaphthen and its *S*-dioxide into thionaphthenopyrazoles is inhibited when a substituent is present in the ortho-position in the phenylhydrazine nucleus but not when the same substituent is in the meta- or para-positions. Certain ortho-substituted thionaphthenopyrazoles have been prepared by an alternative method.

IT has been shown (Barry and McClelland, J., 1935, 471) that the phenylhydrazone of 3-hydroxy-2-acetyl-1-thionaphthen (I) is cyclised in acid media to the corresponding pyrazole (II). The influence of substituents and their position in nucleus A on the formation of pyrazoles from hydrazones of the above type has now been investigated.

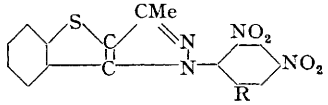
(I.) 

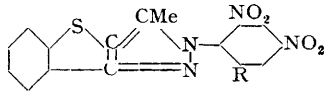
 (II.)

The 2-*nitro*- and 2 : 4-*dinitro-phenylhydrazones* of (I) cannot be cyclised to pyrazoles under conditions effective for pyrazole formation in the unsubstituted phenylhydrazone. This resistance to ring formation might be due either to the polar character of the nitro-group or to an "ortho-effect." That the latter view is correct is suggested by the facile formation of pyrazoles from the 4-*nitro*- and 3-nitro-*phenylhydrazones*, where, if a polar effect was operative, it might be expected to be evident. This view was confirmed by the observation that the 2-*methyl*- and 2-*methoxy-phenylhydrazones* also resist cyclisation and could not be converted into pyrazoles, whereas *pyrazoles* are readily formed from the 4-methyl- and 4-*methoxy-phenylhydrazones* : indeed, ring formation is so rapid in the former case that the 4-methylphenylhydrazone was not isolated, condensation of (I) with *p*-tolylhydrazine hydrochloride giving the pyrazole in one operation. If the inhibition of pyrazole formation were due to polarity, it would be unlikely that groups of so widely differing polar character as nitro-, methyl, and methoxyl would have the same inhibiting effect and exhibit it only when in the 2-position.

Furthermore, although it had been shown (Smiles and Cohen, J., 1930, 406) that the phenylhydrazone of 3-keto-2-acetyl-2 : 3-dihydrothionaphthen 1 : 1-dioxide (I with SO_2 in place of S) is readily converted into a pyrazole, yet it is now found that the 2-*nitro*-, 2 : 4-*dinitro*-, 2-*methyl*-, and 2-*methoxy-phenylhydrazones* of this dioxide cannot be converted into pyrazoles under similar conditions.

Pyrazoles substituted in the *o*-position have been prepared by condensing picryl chloride with 3-methyl-4 : 5-thionaphthenopyrazole and its dioxide. The products may have the structure (III; R = NO_2) or (IV;

(III.) 

 (IV.)

R = NO_2) and the corresponding dioxides. Attempts to obtain the dinitropyrazole from 3-methyl-4 : 5-thionaphthenopyrazole and 2 : 4-dinitrochlorobenzene were unsuccessful, but the dioxide readily condensed with the latter substance, yielding the *pyrazole* (III or IV; R = H, and SO_2 in place of S). It is thus evident that the failure to obtain thionaphthenopyrazoles from *o*-substituted hydrazones is not to be attributed to instability of the pyrazoles preventing their formation, since, provided that the pyrazole ring be first formed, such *o*-substituted compounds can be obtained.

It would appear that the sulphur atom in a phenylhydrazone of the type (I) has also an inhibiting effect on the formation of the pyrazole from it. For instance, benzoylacetone, in which there is no sulphur atom, reacts with phenylhydrazine alone to give 1 : 5-diphenyl-3-methylpyrazole (Fischer and Bülow, *Ber.*, 1885, **18**, 2131; Drumm, *Proc. Roy. Irish Acad.*, 1931, **40**, *B*, 106), whereas 3-hydroxy-2-acetyl-1-thionaphthen yields the phenylhydrazone and only gives the pyrazole (II) in acid media. Further, benzoylacetone condenses with *o*-substituted 2 : 4-dinitrophenylhydrazines to give pyrazoles (Brady, J., 1931, 756), in contrast to 3-hydroxy-2-acetyl-1-thionaphthen which, as described, gives hydrazones not convertible into pyrazoles.

The precise mechanism of this inhibiting effect of the sulphur is not obvious. It may be due either to the extra rigidity which the sulphur bridge confers on the molecule, or to the chemical character of the sulphur atom, or to a combination of both factors.

EXPERIMENTAL.

The required phenylhydrazones were prepared by boiling 3-hydroxy-2-acetyl-1-thionaphthen or 3-keto-2-acetyl-2 : 3-dihydrothionaphthen 1 : 1-dioxide with an approximately equal weight of the appropriate phenylhydrazine in alcohol, except in the case of 2-nitrophenylhydrazine, where the hydrochloride was used instead of the free base.

3-*Hydroxy*-2-*acetyl*-1-*thionaphthen*-2 : 4-*dinitrophenylhydrazone* crystallised from nitrobenzene in dark purple needles, m. p. 279° (Found : C, 51·4; H, 3·5. $C_{16}H_{12}O_5N_4S$ requires C, 51·6; H, 3·2%). The 2 : 4-*dinitrophenylhydrazone* of the 1 : 1-dioxide crystallised from aqueous dioxan in yellow prisms, m. p. 255° (decomp.) (Found : C, 47·6; H, 2·9. $C_{16}H_{12}O_7N_4S$ requires C, 47·5; H, 3·0%); it was also obtained from the corresponding thionaphthenhydrazone by oxidation with hydrogen peroxide (3 c.c. of 100-vol. peroxide in 100 c.c. of glacial acetic acid for 1 g. of hydrazone), the mixture being heated at 100° for ½ hour.

3-*Hydroxy*-2-*acetyl*-1-*thionaphthen*-2-*nitrophenylhydrazone* and its *dioxide* crystallised from glacial acetic acid in red plates, m. p. 225° (Found : C, 59·0; H, 3·9. $C_{16}H_{13}O_3N_3S$ requires C, 58·7; H, 4·0%), and in orange-yellow needles,

m. p. 242° (decomp.) (Found: C, 53·3; H, 3·7. $C_{16}H_{13}O_5N_3S$ requires C, 53·5; H, 3·6%), respectively. The corresponding hydroxyacetylthionaphthen-3-nitrophenylhydrazone, crystallising from alcohol in brown plates, m. p. 225°, was not analysed.

3-*Hydroxy*-2-*acetyl*-1-*thionaphthen*-4-*nitrophenylhydrazone* crystallised from *cyclo*hexanone in brown-red needles, m. p. 256—258° (Found: C, 58·6; H, 4·3; N, 13·0. $C_{16}H_{13}O_3N_3S$ requires C, 58·7; H, 4·0; N, 12·9%). The 2-*methylphenylhydrazone* crystallised from benzene in yellow needles, m. p. 151° (Found: C, 69·0; H, 5·3. $C_{17}H_{16}ON_2S$ requires C, 68·9; H, 5·4%); its *dioxide* formed yellow needles, m. p. 243° (Found: C, 62·1; H, 4·7. $C_{17}H_{16}O_3N_2S$ requires C, 62·2; H, 4·9%), from benzene.

The 2-*methoxyphenylhydrazone* separated from benzene in yellow needles, m. p. 177° (Found: C, 65·1; H, 5·2. $C_{17}H_{16}O_2N_2S$ requires C, 65·4; H, 5·1%); its *dioxide*, crystallised from benzene, had m. p. 202° (Found: C, 59·1; H, 4·6. $C_{17}H_{16}O_4N_2S$ requires C, 59·3; H, 4·6%). The 4-*methoxyphenylhydrazone* formed yellow needles from benzene, m. p. 155° (Found: C, 65·3; H, 5·3%).

Attempted Cyclisation of the 2-*Substituted Phenylhydrazones of* 3-*Hydroxy*-2-*acetyl*-1-*thionaphthen.*—The 2 : 4-dinitrophenylhydrazone (1 g.) was (i) heated under reflux in alcohol (150 c.c.) containing concentrated sulphuric acid (30 c.c.) for 7 hours, (ii) heated in alcohol (100 c.c.) with concentrated sulphuric acid (100 c.c.) on the water-bath for 3 hours (charring), (iii) heated at 100° in glacial acetic acid (50 c.c.) containing concentrated sulphuric acid (10 c.c.) for 3 hours, (iv) heated under reflux in benzene (100 c.c.) with phosphoric oxide (10 g.) for 7 hours. From all these experiments the whole, or most, of the original hydrazone was recovered unchanged. Similar methods failed with the other 2-substituted phenylhydrazones described above.

The facile cyclisation of the phenylhydrazones having the 2-position unsubstituted is exemplified by the preparations of the first four pyrazoles below.

1-(3″-*Nitrophenyl*)-3-*methyl*-4 : 5-2′ : 3′-*thionaphthenopyrazole.*—3-Hydroxy-2-acetyl-1-thionaphthen-3-nitrophenylhydrazone (0·5 g.) was heated under reflux in alcohol (10 c.c.) with a few drops of concentrated sulphuric acid for 3 hours. The product crystallised from acetic acid in cream-coloured needles, m. p. 175° (Found: C, 61·9; H, 3·4. $C_{16}H_{11}O_2N_3S$ requires C, 62·1; H, 3·6%). The corresponding S-*dioxide*, obtained by oxidation with hydrogen peroxide in acetic acid at 100° for 1 hour, formed pale yellow prisms from glacial acetic acid; m. p. 185° (Found: C, 56·5; H, 3·1. $C_{16}H_{11}O_4N_3S$ requires C, 56·3; H, 3·2%). The corresponding *pyrazole* from the 4-nitrophenylhydrazone (1 hr.'s boiling in acetic acid with a little sulphuric acid) crystallised from bromobenzene in yellow needles, m. p. 215° (Found: N, 13·4. $C_{16}H_{11}O_2N_3S$ requires N, 13·6%).

1-(4″-*Methylphenyl*)-3-*methyl*-4 : 5-2′ : 3′-*thionaphthenopyrazole.*—When equal weights of 3-hydroxy-2-acetyl-1-thionaphthen and 4-methylphenylhydrazine hydrochloride were heated in alcohol under reflux for 2—3 hours this *substance* was formed, crystallising from alcohol in colourless needles, m. p. 108—110° (Found: C, 73·0; H, 4·8. $C_{17}H_{14}N_2S$ requires C, 73·4; H, 5·0%).

1-(4″-*Methoxyphenyl*)-3-*methyl*-4 : 5-2′ : 3′-*thionaphthenopyrazole* was produced from the corresponding hydrazone by boiling for 1 hour in alcohol with a few drops of sulphuric acid. The product, isolated by adding water, crystallised from acetic acid (charcoal) in colourless needles, m. p. 126° (Found: C, 69·2; H, 4·7. $C_{17}H_{14}ON_2S$ requires C, 69·4; H, 4·8%).

1-(2″ : 4″ : 6″-*Trinitrophenyl*)-3 (or 5)-*methyl*-4 : 5-2′ : 3′ (or 3 : 4-3′ : 2′)-*thionaphthenopyrazole.*—3-Methyl-4 : 5-thionaphthenopyrazole (2 g.) was heated under reflux in alcohol (20 c.c.) containing sodium (0·2 g.) for 2 hours with 2 : 4 : 6-trinitrochlorobenzene (3 g.), and the solution evaporated to dryness. The residue was washed with warm water, and crystallised from glacial acetic acid in yellow needles, m. p. 236° (Found: C, 48·0; H, 2·3. $C_{16}H_9O_6N_5S$ requires C, 48·1; H, 2·2%). The S-*dioxide*, prepared similarly, crystallised from acetic acid in yellow prisms, m. p. 230° (Found: C, 44·65; H, 2·3. $C_{16}H_9O_8N_5S$ requires C, 44·5; H, 2·1%).

The S-*dioxide* of the 2 : 4-dinitrophenyl analogue was prepared by adding 2 : 4-dinitrochlorobenzene (5 g.) in alcohol (50 c.c.) and 3-methyl-4 : 5-thionaphthenopyrazole S-dioxide (5 g.) to alcohol (50 c.c.) containing sodium (0·5 g.) and boiling the mixture for 3 hours. The product which separated after filtration and cooling was crystallised from glacial acetic acid (charcoal), and had m. p. 238° (Found: C, 49·6; H, 2·9; N, 14·5. $C_{16}H_{10}O_6N_4S$ requires C, 49·7; H, 2·6; N, 14·5%).

KING'S COLLEGE, LONDON.

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