

STUDIES ON THE WILLGERODT-KINDLER REACTION.
MORPHOLINO-THIOPHENES FROM ACETYLENE-KETONES,
FROM β -DIKETONES AND FROM ANALOGOUS COMPOUNDS .

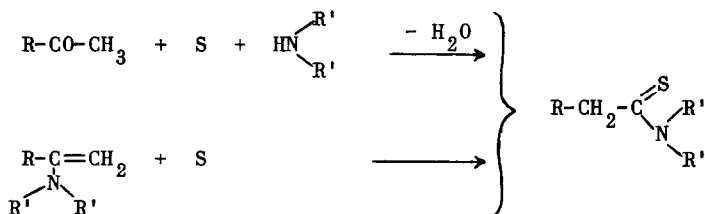
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Though the Willgerodt-Kindler (W-K) reaction has been widely studied (1), many problems related to it are still unsolved. We report now the results of some experiments carried out on acetylene-ketones, on β -diketones and, more generally, on bifunctional compounds with suitable structures, under the well-known conditions of the W-K reaction.

Since we have noticed that under these conditions enamine derivatives were formed (see Scheme A : compounds II and IV), we investigated at first the behaviour of some simple compounds of this class :



TABLE(†)

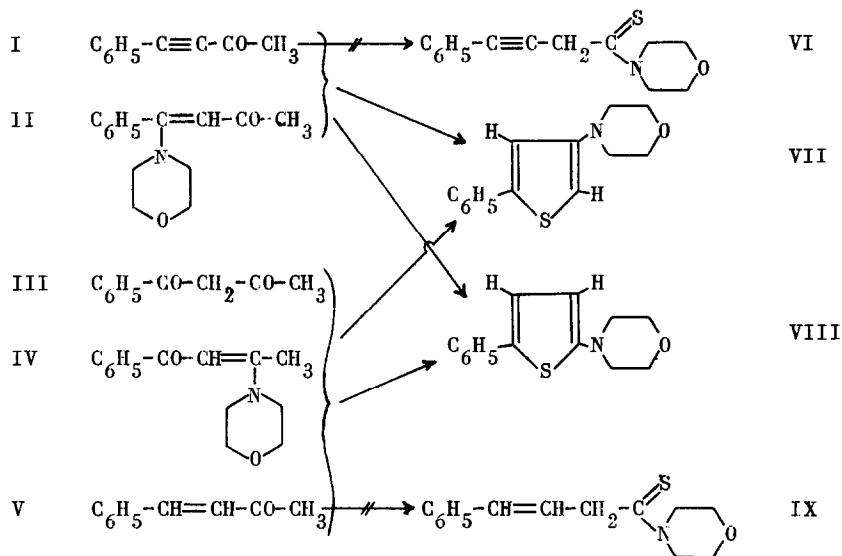
Reactants		Products	Yields
$C_6H_5-CO-CH_3$	+ S + Morph.	$C_6H_5-CH_2-C \begin{matrix} \diagup S \\ \diagdown \text{Morph.} \end{matrix}$	75%
$C_6H_5-C \begin{matrix} \diagup CH_2 \\ \diagdown \text{Morph.} \end{matrix}$	+ S + Morph.	$C_6H_5-CH_2-C \begin{matrix} \diagup S \\ \diagdown \text{Morph.} \end{matrix}$	75%
$CH_3-CH_2-CO-CH_2-CH_3$	+ S + Morph.	$CH_3-(CH_2)_3-C \begin{matrix} \diagup S \\ \diagdown \text{Morph.} \end{matrix}$	55%
$CH_3-CH_2-C \begin{matrix} \diagup CH-CH_3 \\ \diagdown \text{Morph.} \end{matrix}$	+ S + Morph.	(b.p. $0,1 = 130-140^\circ$)	35%
$C_6H_5-CO-CH=C \begin{matrix} \diagup H \\ \diagdown \text{Morph.} \end{matrix}$	+ S + Morph.	$C_6H_5-CO-CH_2-C \begin{matrix} \diagup S \\ \diagdown \text{Morph.} \end{matrix}$	60%

(†) All the reactions were carried out at 125° for 4 hours.

From the experiments illustrated in the above Table new evidence has been gathered on the analogy between enamines and carbonyl compounds⁽⁰⁾.

(⁰) At the onset of this research only a single enamine derivative: 1-morpholino-cyclohexene, had been subjected to the reaction with sulphur and morpholine (2). Lately the possibility of transforming enamines into thio-amides by reaction with sulphur in dimethyl-formamid at room temperature was announced (3).

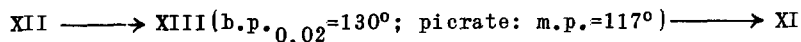
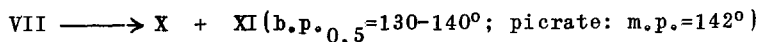
SCHEME A



Acetyl-phenyl-acetylene (I) had been subjected previously to the W-K reaction and to the resulting product D. Nightingale and R. A. Carpenter (4) had assigned the structure of 4-phenyl-3-butyne-thiocarboxylic acid morpholide (VI). We have now established that the principal product of this reaction is instead 2-phenyl-4-N-morpholino-thiophene (VII) together with small quantities of its isomer VIII. Elemental analysis and molecular weight determination of the mixture as obtained by the American Authors (M.p. 79-80°) are consistent with empirical formula $\text{C}_{14}\text{H}_{15}\text{NOS}$. On the other hand the I.R. absorption spectrum shows transparency in the triple bond region, and gas-chromatography indicates the material to be a mixture of VII (90%) and VIII (10%). Column chromatography on alumina (benzene-petroleum ether 1:4)

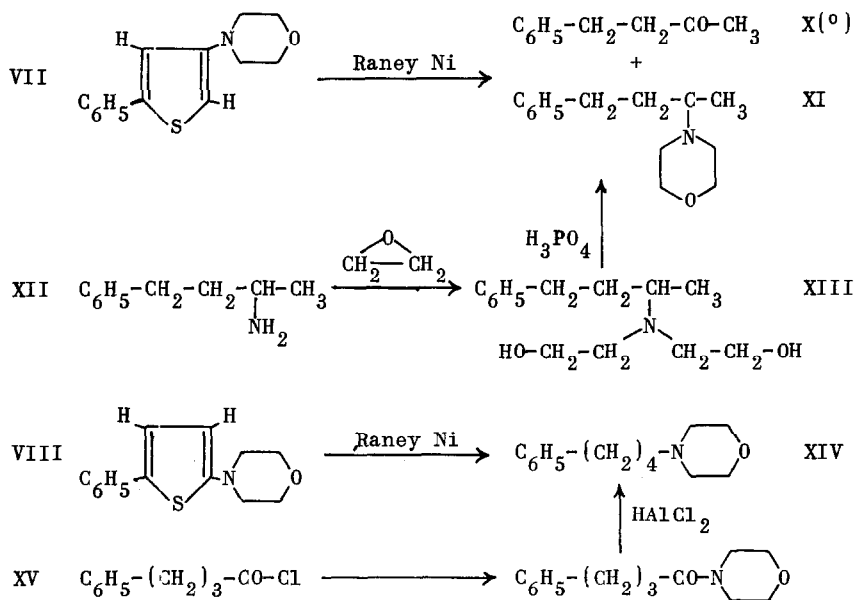
yielded VII as a pure solid melting at 87°C. N.m.r. analysis of VII furnished the following data: H(3): $\tau=3,7(d)$, $J_{3-5}=1,5$ c/s. H(5): $\tau=4,02(d)$, $J_{3-5}=1,5$ c/s. C_6H_5 : $\tau=2,43-2,92(m)$. CH_2-N-CH_2 : $\tau=7,03(m)$. CH_2-O-CH_2 : $\tau=6,28(m)$.

Structure VII was conclusively assigned on the ground of the transformations:

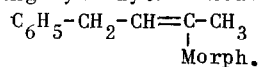


illustrated in Scheme B.

SCHEME B



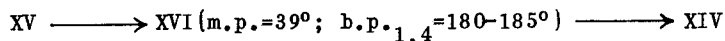
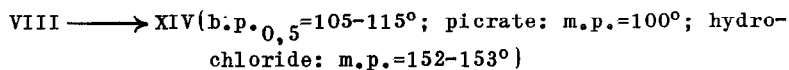
(°) This may be considered as a new example of formation of a ketone from a Raney-Nickel desulphuration reaction (5). The intermediate undergoing hydrolytic cleavage is presumably:



The reaction of benzoylacetone (III) in the same conditions as for acetyl-phenyl-acetylene (I) furnished the same two isomeric thiophene derivatives (VII and VIII), though in inverted ratios. From a typical run 30% of VIII, together with about 5% of VII and traces of phenyl-aceto-thiomorpholide and benzoylmorpholine were obtained. The main product (VIII) of this reaction was obtained as a solid melting at 132°C and its I.R. absorption spectrum shows transparency in the triple bond region. N.m.r. analysis of VIII furnished the following data:

H(3): $\tau=3(d)$, $J_{3-4}=4$ c/s. H(4): $\tau=3,9(d)$, $J_{3-4}=4$ c/s. C_6H_5 : $\tau=2,5-2,85(m)$. CH_2-N-CH_2 : $\tau=6,95(m)$. CH_2-O-CH_2 : $\tau=6,25(m)$.

Structure VIII was conclusively assigned on the ground of the transformations:



illustrated in Scheme B.

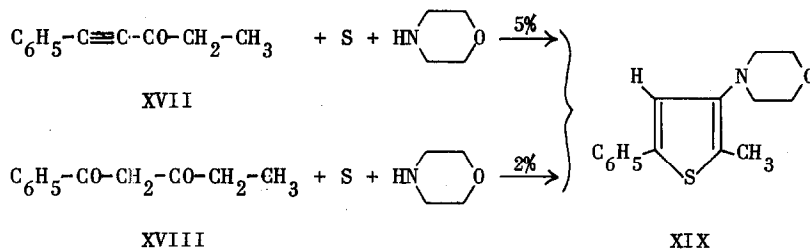
Comparable results were obtained from the reaction of the enamine IV (6) in the W-K conditions (Scheme A).

Since the melting point of 2-N-morpholino-5-phenyl-thiophene (VIII) was found to be identical with that reported for a substance previously described (4) as 4-phenyl-3-butene-thiocarboxylic acid morpholide (IX) and prepared from benzalacetone (V) (Scheme A), we decided to reinvestigate this reaction. We found that the development of this reaction is very similar to that observed on benzoyl-acetone (III): the main resulting product (m.p.=132°) is identical with the thiophene derivative VIII; it is accompanied by a trace of VII.

2-Phenyl-4-hydroxy-thiophene (XX) (7), which could be considered as an intermediate in the reaction leading to VII, reacts smoothly with morpholine furnishing VII in the same yields (40-

50%) observed with I.

Two more ketones: XVII and XVIII, homologues of acetyl-phenyl-acetylene and of benzoylacetone respectively, were examined.



The structure of 2-methyl-3-N-morpholino-5-Phenyl-thiophene was assigned to XIX on the ground of the following n.m.r. data:

H(4): $\tau=3$ (s). CH₃: $\tau=7,75$ (s). C₆H₅: $\tau=2,5-2,9$ (m). CH₂-N-CH₂: $\tau=7,23$ (m). CH₂-O-CH₂: $\tau=6,33$ (m).

The reaction illustrated above appears to be a useful tool for reaching a better understanding of the W-K reaction and particularly for establishing positions undergoing attack by sulphur and for giving evidence of participation of the secondary amine in the intermediate steps of the process. The reaction moreover shows promise as a new general method for the preparation of some amino-thiophene derivatives.

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