

SYNTHESIS OF 2,3- AND 2,7-DIHYDROTHIEPINES

D.N. Reinhoudt* and Miss C.G. Leliveld

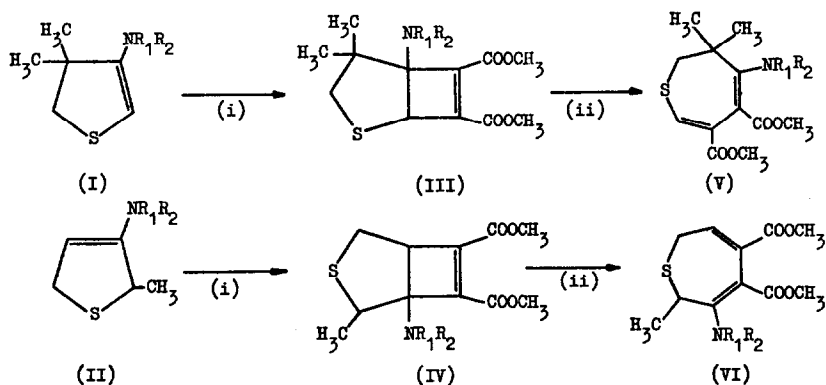
KONINKLIJKE/SHELL-LABORATORIUM, AMSTERDAM

(Shell Research N.V.), Amsterdam-N, The Netherlands

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One of the methods used in carbocyclic chemistry to achieve ring enlargement consists in the cycloaddition of an activated acetylene such as (di)methyl acetylene-(di)carboxylate to an enamine of a cyclic ketone¹. In a subsequent step the cyclobutene ring is opened simply by heating the bicyclic intermediate⁺.

We have applied this method to the synthesis of dihydrothiepinines, a novel class of compounds⁺⁺. The cycloaddition of enamines of (alkylated) tetrahydrothiophen-3-ones (I and II)⁴ to dimethyl acetylenedicarboxylate in diethyl ether as a solvent proceeded smoothly at room temperature and yielded crystalline 2-(or 3-)thiabicyclo [3.2.0] hept-6-ene derivatives (III and IV). Upon being heated at 100 °C in dioxane these products gave the corresponding dihydrothiepinines (V and VI) in an overall yield of 40-90%.



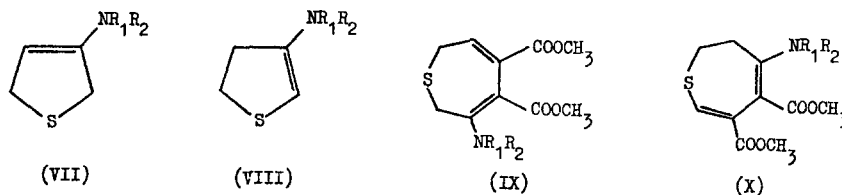
(i) 1 eq. dimethyl acetylenedicarboxylate in diethyl ether, 20 °C; 16 h

(ii) dioxane; 100 °C; 2 h

The compounds were identified by the NMR signals of their vinyl protons: compounds of type (V) gave a singlet in the δ 7.0-7.6 ppm range and those of type (VI) a triplet in the δ 6.6-7.0 ppm range ($J \sim 8$ Hz).

A further investigation of the general characteristics of the reaction revealed the following:

- (a) In the cycloaddition the enamine double bond is more reactive in the 4,5- than in the 3,4-position. This was concluded from the reactions with enamines of tetrahydrothiophen-3-one (mixtures of (VII) and (VIII), ratio ~ 2 : 1). A mixture of 2,7- and 2,3-dihydrothiepin (IX and X) was obtained in a ratio ~ 1 : 2. Since the enamines are not interconvertible under the conditions applied in this experiment, this result indicates that the 2,3-dihydro compound (VIII) is about four times as reactive as its 2,5-dihydro isomer (VII).



- (b) Alkyl groups adjacent to the enamine double bond lower the rate of cycloaddition.
 (c) As expected, the effect of the secondary amino group on the rate of cycloaddition decreases in the order: pyrrolidino > morpholino > piperidino.
 (d) Dimethyl acetylenedicarboxylate is more reactive than methyl propiolate, which reacts only with pyrrolidine enamines.

Acid-catalysed hydrolysis of the enamine moiety gave enols stabilized by hydrogen bonding, and/or the corresponding ketones. These compounds can be oxidized by *m*-chloroperbenzoic acid at room temperature to the corresponding sulphones.

REFERENCES AND FOOTNOTES

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- + Recently, similar reactions have been used for the synthesis of benzazepines (ref. 2).
 ++ Monocyclic thiepin and their dihydro derivatives have not been described; owing to their anti-aromatic character, thiepin is expected to be a reactive species (ref. 3).