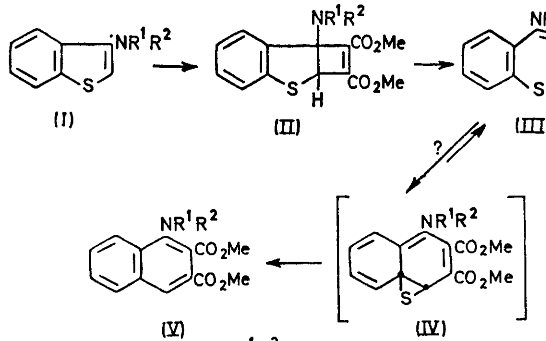
Synthesis of Benzo[*b*]thiepins, a Class of 12π-Electron Heterocycles

By D. N. REINHOUDT* and MRS. C. G. KOUWENHOVEN

[*Koninklijke/Shell-Laboratorium* (*Shell Research N.V.*), *Amsterdam, The Netherlands*]

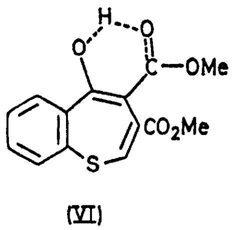
Summary 3,4-Dimethoxycarbonyl-5-pyrrolidin-1-ylbenzo[*b*]thiepin has been prepared in a one-step synthesis by cycloaddition of 3-pyrrolidin-1-ylbenzo[*b*]thiophen (Ia) to dimethyl acetylenedicarboxylate; upon being heated, benzo[*b*]thiepins of this type rearrange to give naphthalenes and upon oxidation they yield thermally stable 1,1-dioxides.

HETEROCYCLIC compounds containing 4*n*π-electrons have been studied extensively because of their formal anti-aromatic character.[1] Only a few thiepins have been described compared with the number of azepines and oxepins reported.[2] The generally observed instability of the thiepins is clearly borne out by the fact that in several attempted syntheses, even under mild conditions, sulphur was extruded and the corresponding aromatic compounds were formed.[3]

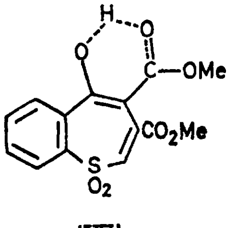


a; NR^1R^2 = pyrrolidin-1-yl
b; NR^1R^2 = piperidin-1-yl

We here report on the synthesis and reactivity of stable benzo[*b*]thiepins. Their preparation is modelled upon a cycloaddition between the enamine derivatives of tetrahydrothiophen-3-ones and activated acetylenes in diethyl ether.[4] Application of this reaction (16 h; 37°) to 3-pyrrolidin-1-ylbenzo[*b*]thiophen (Ia),[5] in which the enamine double bond constitutes part of an aromatic 10π-electron system, gave the benzo[*b*]thiepin (IIIa) (60%),† *via* an intermediate cycloadduct (II).



(VI)



(VII)

The formation of the intermediate (IIa) was inferred from the ^{1}H n.m.r. spectrum of the reaction mixture (Et_2O; -20 °C), which contained a signal characteristic of a bridgehead hydrogen (1-H)[6] at δ 4·75 p.p.m.‡ The ^{1}H n.m.r. spectrum of benzo[*b*]thiepin (IIIa) exhibits a signal at δ 7·00 p.p.m., in the range expected for the vinylic proton in this compound. Prolonged heating of the benzo[*b*]thiepin (IIIa) in dioxan at 100° resulted in extrusion of the sulphur, possibly *via* the valence isomer (IV),[7] and the formation of a naphthalene derivative (Va).

When subjected to cycloaddition conditions (16 h refluxing in dioxan) 4-piperidin-1-ylbenzo[*b*]thiepin (Ib) was converted directly into the naphthalene. This is in line with the fact that the double bond in this particular enamine is less reactive towards cycloaddition than the double bond in (Ia). Hence, unlike the pyrrolidine enamine, the piperidine compound enters into the cycloaddition reaction only at temperatures which favour subsequent extrusion of sulphur.

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† All new compounds had satisfactory elemental analyses and their spectral data were in agreement with the proposed structures.

‡ In $CDCl_3$ solution with Me_4Si as the internal reference.

Acid-catalysed hydrolysis of the enamine part of (IIIa) gave, under mild conditions, the corresponding benzo[*b*]thiepin-5-ol (VI) in quantitative yield. Rather surprisingly, the ^{1}H n.m.r. and i.r. spectra revealed this compound to be present in its enolic form. Apparently, the enolic form, stabilized by hydrogen bonding, is energetically favoured over the keto-species, which, unlike the former, has no formal anti-aromatic structure.[3a]

Upon being heated in an inert solvent, (VI) rearranges without loss of sulphur to give 2,3-dimethoxycarbonyl-4-mercaptonaphthalen-1-ol.

The rapid oxidation of (VI) with 2 equiv. of *m*-chloroperbenzoic acid to the corresponding sulphone (VII) provides a useful synthesis of benzo[*b*]thiepin 1,1-dioxides, thermally stable 10π-electron heterocycles.

We have shown that the thiepin system is stabilized by electron-withdrawing substituents. Similar observations have been reported for thieno[3,4-*d*]- and furo[3,4-*d*]-thiepins[8] and for 3,5-diacetoxy-4-phenylbenzo[*b*]thiepin.[7] The increase in stability can be attributed to a decrease in electron density of the 8π-electron system, as a result of which the formal anti-aromatic character is reduced.

(*Received*, 15*th September* 1972; *Com.* 1566.)

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[5] Compound (Ib) was prepared by G. Van Zijl, D. C. De Jongh, V. L. Heasley, and J. W. Van Dyke, *J. Org. Chem.*, 1961, **26**, 4946; (Ia) was prepared by an analogous route from benzo[*b*]thiophen.

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