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THE ADDITION OF DIMETHYL ACETYLENEDICARBOXYLATE TO THIAZOLES: AN N.M.R. STUDY OF THE STRUCTURE OF THE ADDUCTS

D. H. Reid and F. S. Skelton

Department of Chemistry, St. Salvator's College,

The University, St. Andrews

and

W. Bonthrone

"Shell" Research Ltd., Milstead Laboratory of Chemical Enzymology,

Sittingbourne, Kent.

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Pyridine reacts with dimethyl acetylenedicarboxylate in methanol to give inter al., trimethyl indolizine-1,2,3-tricarboxylate.[1] We have, therefore, examined the addition of dimethyl acetylenedicarboxylate to various thiazoles with a view to finding a satisfactory preparative route to pyrrolo[2,1-b]thiazole,[2] and present here a preliminary summary of some of our findings.

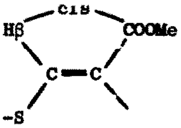
Dimethyl acetylenedicarboxylate was allowed to react with the thiazoles at room temperature in 2:1 molecular proportions, usually for 3-4 days. The outcome of the reactions is markedly solvent-dependent. Two major products were isolated from each thiazole in yields depending on the solvent employed.

2,4-Dimethylthiazole in dimethylformamide gave as major product a 2:1 adduct (37%),[3] orange-red rods, m.p. 145.5 - 147°, λ_{max} 215 broad, 239 broad, 295, and 446 mμ[4] (log ε 4.09, 4.13, 4.24, and 3.72), for which we propose the [3,4,0]-bicyclic structure (I).[5] Its n.m.r. spectrum[6] shows a group of signals (12H) in the range δ3.71 - 3.92 (4 COOMe), a singlet (3H) at δ1.43 (CH_3), a weakly resolved doublet (3H) at δ2.02 (CH_3), and a broad unresolved line (1H) at δ5.70 (vinylic). The methyl group at δ2.02 is weakly coupled (J = 1.1c./sec.) to the vinyl proton, and corresponds to the 4-methyl group of the reactant. The other methyl group must reside on sp^3 carbon to account for its relatively shielded environment; its chemical shift compares favourably with that (δ1.58) of the 2-methyl group in 2,3-dimethyl-2,3-dihydrobenzothiazole.

In contrast to the foregoing, we assign structures (IIa or b), (IIIa or b), and (IVa or b) to the major products from 2-methylthiazole, thiazole, and 4-methylthiazole, respectively, in dimethylformamide. The product from 2-methylthiazole (36%) formed orange prisms, m.p. 159.5 - 161°, λ_{max} 224, 283, and 428 mμ (log ε 4.11, 4.32, and 3.64), whose n.m.r. spectrum shows a group of signals (12H) at δ3.72 - 3.86 (4 COOMe), a singlet (3H) at δ2.67 (CH_3), and two doublets of an AB system centred at δ6.05 and 6.74 (J ~ 5c./sec.). The methyl resonance at δ2.67 is incompatible with an angular methyl group as present in (I), and requires the methyl group to be vinylic. These data allow only two possible structures for this adduct, i.e., the [5,2,0]-bicyclic structure (IIa) and the nine-membered monocyclic structure (IIb). The latter appears less likely on stereochemical grounds but cannot be excluded with certainty on the available evidence.

The product from thiazole (20%) formed orange prisms, m.p. 147.5 - 149°, λ_{max} 225, 282, and 430 (log ε 4.16, 4.33, and 3.63). The n.m.r. spectrum shows a group of signals (12H) at δ3.72 - 3.92 (4 COOMe), two doublets of an AB system centred at δ6.02 and 6.52 (J ~ 4.75 c/sec.), and a singlet (1H) at δ8.13. The low-field position of the singlet requires the proton to be vinylic and therefore to reside on what was C-2 of thiazole. This limits the structure of the adduct to either (IIIa) or (IIIb). On the basis of similar reasoning the adduct from 4-methylthiazole, obtained (43%) as orange tablets, m.p. 219 - 224° (decomp.), λ_{max} 227, 285, and 441 mμ (log ε 4.18, 4.33, and 3.65)*, is assigned structure (IVa) or (IVb).

The n.m.r. spectra of open-chain and cyclic model compounds containing the structure



all showed strong deshielding of the β-proton, e.g., in methyl trans-β-benzylthioacrylate (δ7.70), dimethyl ethylthiomethylenemalonate (δ8.33), and dimethyl 2-methylthiophene -3,4-dicarboxylate (δ7.68). Also, the 2-methyl group of dimethyl 2-methylthiophene-3,4-dicarboxylate has a chemical shift (δ2.53) similar in magnitude to that of the ring-methyl group in compound (II).

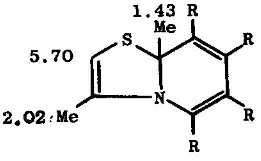
A radically different course was followed when the reactions were performed in methanol or acetonitrile. 2-Alkyl-substituted thiazoles formed 2:1 adducts containing seven-membered rings by addition involving nitrogen and the 2-alkyl group. The product from 2-ethylthiazole, best obtained (10%) using acetonitrile, formed yellow prisms, m.p. 206 - 208°, λ_{max} c. 215 very broad and 450 mμ (log ε 3.94 and 4.49), for which the evidence favours structure (V). The n.m.r. spectrum shows a group of signals (12H) at δ3.60 - 3.85 (4 COOMe), two doublets of an AB system centred at δ6.29 and 6.72 (J~ 4.5c./sec.), two doublets of a second AB system centred at δ5.36 and 5.66 (J~ 5.5c./sec.), and a sharp singlet (3H) at δ1.82 (CH_3). The methylene group of the 2-ethyl substituent must have reacted because methylene (and methine) signals are absent, and the methyl signal at δ1.82 is unsplit. These data strongly suggest that a seven-membered ring has been formed. The adjacent pair of thiazole ring protons in structure (V) accounts for one of the AB systems. The other must arise from an adjacent pair in the newly formed ring. The absence of splitting of the methyl signal also demonstrates thatthe methyl group is vinylic. The seven-membered ring must accomodate a vinylic methyl group, an AB pair of protons, and two double bonds. Two structures only, (V) and (VI), satisfy these requirements. Supplementary evidence favours the former. This follows. 2-Methylthiazole in methanol gave an analogous product (1.3%), yellow prisms m.p., 172.5 - 175.5°, λ_{max} c. 220 very broad and 441 mμ (log ε 3.83 and 4.51). The double bond distribution must be the same in both adducts since their ultraviolet and visible spectra are very similar. The n.m.r. spectrum of the adduct from 2-methylthiazole shows the same pattern of signals as that from compound (V) with the only difference that the ring-methyl signal of the latter is replaced by a singlet (1H) at δ5.12. These data rule out structures with double bond distribution as in (VI) and establish structures (V) and (VII) for the adducts from 2-ethylthiazole and 2-methylthiazole. On the basis of similar considerations analogous [3,5,0]-bicyclic structures have been assigned to the adduct (15%) from 2,4-dimethylthiazole, yellow prisms, m.p. 154 - 156°, and that (73%) from 2-methylbenzothiazole, lemon-yellow prisms, m.p. 201 - 211°, both prepared in methanol.

Thiazoles unsubstituted at position 2 reacted in methanol to give pyrrolo[2,1-b]thiazole derivatives. Thiazole gave trimethyl pyrrolo-[2,1-b]thiazole-5,6,7-tricarboxylate (VIII) (8.5%), colourless prisms, m.p. 154 - 157°, giving a positive Ehrlich test after being boiled with concentrated hydrochloric acid in ethanol. The n.m.r. spectrum showed a singlet (6H) at δ3.90 (5- and 7-COOMe), a singlet (3H) at δ4.03 (6-COOMe), and an AB pair of doublets at δ7.11 (H-2) and δ8.37 (H-3) (J ~ 4.5c./sec.).

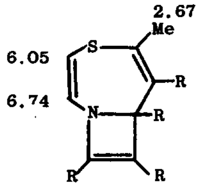
Benzothiazole under similar conditions afforded trimethyl pyrrolo[2,1-b]-benzothiazole-1,2,3-tricarboxylate (40%), colourless prisms, m.p. 135 - 136°.

Dimethyl acetylenedicarboxylate also forms adducts with Δ^2-thiazolines. The structure of these is under investigation.

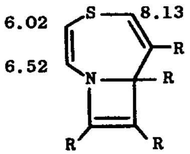
Satisfactory analytical data were obtained for all compounds cited.



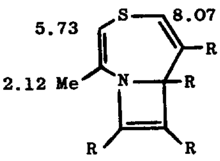
(I)



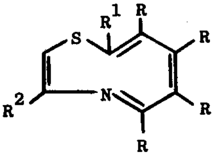
(IIa)



(IIIa)



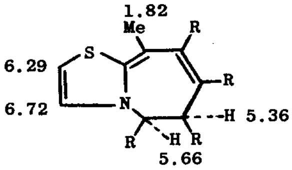
(IVa)



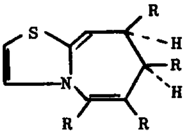
(IIb) R^1 = Me; R^2 = H

(IIIb) R^1 = R^2 = H

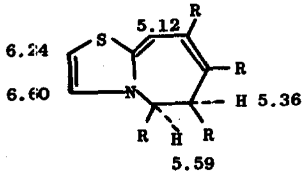
(IVb) R^1 = H; R^2 = Me



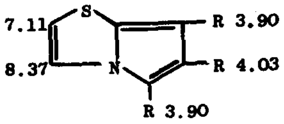
(V)



(VI)



(VII)



(VIII)

R = COOMe in all cases

REFERENCES

1. O. Diels and R. Meyer, Liebig's Ann. Chem., 513, 129 (1934).

2. Pyrrolo[2,1-b]thiazole has been prepared in low yield by successive reaction of 2-thiazolyl lithium with epichlorohydrin, hydrolysis, and cyclisation in boiling t-butanol (B. B. Molloy and D. H. Reid, unpublished results).

3. Yields are based on the quantity of the thiazole allowed to react.

4. Ultraviolet spectra were measured for methanol solutions.

5. Numbers attached peripherally to formulae refer to the chemical shifts of the corresponding protons.

6. N.m.r. spectra were run on a Varian A-60 instrument, using $CDCl_3$ as solvent and Me_4Si as internal reference. Chemical shifts (δ) are given in parts per million downfield from the T.M.S. signal.