49. Structures of Addition Products of Acetylenedicarboxylic Acid Esters with Various Dinucleophiles. An Application of C,H-Spin-Coupling Constants¹)

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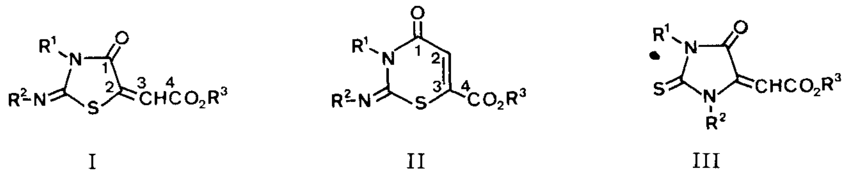
Summary

Heterocyclic compounds obtained by addition of acetylenedicarboxylic acid esters to thioureas, cyclic amidines and *o*-difunctionalized aromatic systems have been studied by ^{13}C-NMR. In particular, C,H-spin-coupling constants over two and three bonds were used to differentiate between the various constitutional isomers and to establish the configuration of trisubstituted exocyclic C,C-double bonds. The configurational significance and diagnostic value of vicinal *cis* and *trans* C,H-spin coupling is again demonstrated in the present series.

1. Introduction. - The reaction of acetylenedicarboxylic acid esters with dinucleophiles offers a versatile approach to the synthesis of a variety of heterocyclic systems, but is often beset of the problem of structural ambiguities [2] [3]. The reaction of substituted thioureas with acetylenedicarboxylates, *e.g.*, has been claimed variously to yield thiazolidinones I [4] [5] or dihydro-thiazinones II [6] [7] or, in one case, even a thioximidazolidinone III [8] *(Scheme 1)*. Chemical proof in favour of I was obtained by condensation of a thiazolidinone with ethyl glyoxylate under acidic conditions [5] [9] [10]. However, this evidence cannot be

*Scheme 1*²)



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¹) ^{13}C-NMR. Spectroscopy, Part 19. For Part 18 see [1].

²) For convenience and better understanding of the spectroscopic data only the four C-atoms of the acetylenedicarboxylate moiety in the compounds are numbered.

considered as unambiguous; this is also true for all other chemical reactions with the addition products, since rearrangements in such processes cannot be ruled out [11] [12].

Further, even assuming that the ring size has been correctly established, the configuration of the exocyclic double bond in I has to be determined. In two cases (**1** and **6**) the five-membered ring structure with (*Z*)-configuration of the exocyclic double bond was established by X-ray crystal analysis [13] [14]. However, these results cannot be generalized.

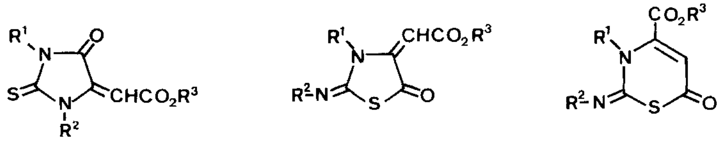
For these reasons we looked for a fast and economic method of general applicability to determine the constitution and configuration of the heterocyclic products obtained from the addition of acetylenedicarboxylates to various dinucleophiles.

In a previous paper [15] we have demonstrated that the configuration of trisubstituted alkenes can be conveniently determined by the use of vicinal $^{13}C,^{1}H$-coupling constants. Based upon a large amount of experimental data (*cf.* also [16]) it is now possible to establish the double bond configuration even in cases where only one of the stereoisomers is available. Furthermore, improved instrumentation of ^{13}C-NMR. spectroscopy in terms of increased sensitivity and larger computer memory have facilitated the routine determination of accurate C,H-coupling data even in rather dilute solutions. This report is an application and extension of our earlier study [15], to the above-mentioned heterocyclic systems.

2. Experimental Results and Discussion. - The five-membered heterocycles **1**-**9** of type I obtained from substituted thioureas and similar substrates with acetylenedicarboxylates are listed in *Table 1.* The ^{13}C-NMR. data of these compounds include *vicinal* (three-bond) and *geminal* (two-bond) C,H-coupling constants, and selected chemical shifts of the fragment originating from the acetylenedicarboxylate moiety[2]). The corresponding data for some six-membered heterocyclic compounds of type II (pyrimidines **16** and **17**, and thiazines **18** and **19**) are summarized in *Table 2.* Finally, the structures and NMR. data of the condensation products **20**-**27** from *o*-difunctionalized aromatic substrates and acetylenedicarboxylates are presented in *Table 3.*

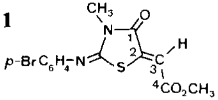
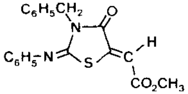
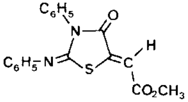
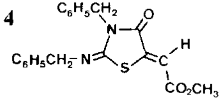
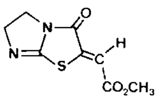
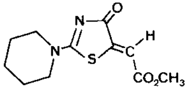
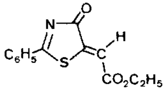
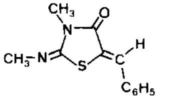
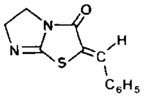
The chemical shift range of the carbonyl groups in compounds **1**-**7** rules out the thioxoimidazolidinone structure III *(Scheme 2)*, wherein the resonance of the thiocarbonyl C-atom is expected to be at approximately 190 ppm [17]. Thiolactone structures IV and V are eliminated by similar chemical shift considerations [17] as well as for chemical reasons (greater nucleophilicity of the sulfur atom in thioureas).

Scheme 2



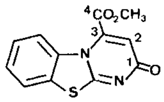
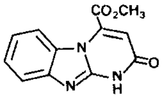
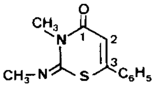
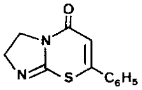
III IV V

Table 1. *Selected C, H-Coupling Constants* J *[Hz] and* ^{13}C *Chemical Shifts* δ *[ppm,* $CDCl_3$*]*

Compound[2])	$^3J(1,H-C(3))$[a])	$^3J(1,NC-H)$	$^3J(4,OC-H)$	$^2J(2,H-C(3))$	$^2J(4,H-C(3))$	$\delta(C(1))$	$\delta(C(2))$	$\delta(C(3))$	$\delta(C(4))$
1 	5.3	2.6	3.9	1.8	1.2	164.4	141.0	116.1	165.8
2 	5.0	3.9	3.7	1.5	≤ 1.3	164.4	141.4	115.9	165.9
3 	5.0	-	3.7	≤ 1.3	≤ 1.3	164.1	141.2	116.2	165.9
4 	4.9	*ca.* 4.9	3.6	≤ 1.3	≤ 1.3	164.4	141.0	115.5	166.1
5[b]) 	5.9	≤ 1.0	*ca.* 3.6	1.9	≤ 1.3	155.6	146.5	113.6	163.9
6 	3.6	-	3.6	2.5	≤ 1.3	178.2	147.0	116.0	166.5
7 	4.8	-	3.1	2.0	1.0	181.2	143.0	122.8	165.1
8 	6.4	2.5	-	≤ 1.3	-[c])	166.0	121.2	129.6– 128.6	-[c])
9[b]) 	6.3	≤ 1.0	-	≤ 1.0	-[c])	157.2	125.9	128.2– 127.9	-[c])

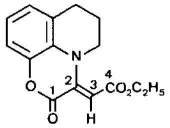
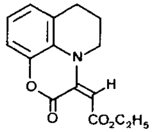
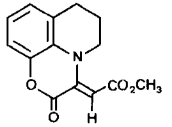
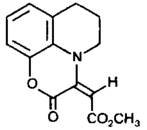
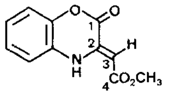
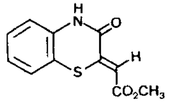
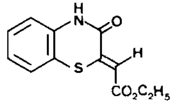
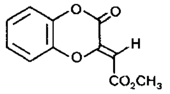
[a]) $^3J(1,H-C(3)) = {}^3J(C(1),H-C(3))$. [b]) In $(CD_3)_2SO/CDCl_3$ *ca.* 1:1. [c]) Not determined.

Table 2. *Selected C,H-Coupling Constants* J *[Hz] and* ^{13}C *Chemical Shifts* δ *[ppm,* $(CD_3)_2SO/CDCl_3$ *ca. 1:1]*

Compound²)	$^2J(1,H-C(2))$a)	$^2J(3,H-C(2))$	$^3J(4,H-C(2))$	$^3J(1,NC-H)$	$^3J(4,OC-H)$	δ(C(1))	δ(C(2))	δ(C(3))	δ(C(4))
16b) 	≤ 1.0	3.9	4.3	-	3.9	165.3	112.9	138.6	161.1
17 	≤ 1.0	3.0	4.2	-	*ca.* 4.2	160.2	108.1	135.9	158.8
18c) 	≤ 1.3	-d)	-d)	2.5	-	162.7	114.1	145.6	-d)
19 	≤ 1.0	-d)	-d)	≤ 1.0	-	158.7	113.0	145.6	-d)

a) $^2J(1,H-C(2)) = {}^2J(C(1),H-C(2))$. b) In $(CD_3)_2SO$. c) In $CDCl_3$. d) Not determined.

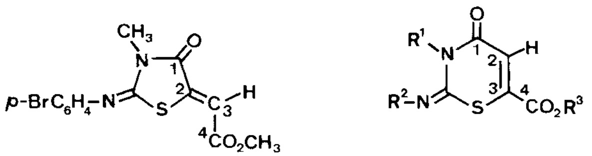
Table 3. *Selected C,H-Coupling Constants* J *[Hz] and* ^{13}*C Chemical Shifts* δ *[ppm, CDCl$_3$]*

Compound[2]		$^{3}J(1,H-C(3))$[a]	$^{3}J(4,OC-H)$	$^{2}J(2,H-C(3))$	$^{2}J(4,H-C(3))$	others	δ(C(1))	δ(C(2))	δ(C(3))	δ(C(4))
20		5.6	3.1	–[c]	1.3	–	156.8	135.5	95.2	165.0
21		11.3	*ca.* 3.0	–[c]	–[c]	–	155.0	132.6	100.4	166.7
22		5.6	4.0	–[c]	1.5	–	156.9	135.7	94.9	165.6
23		–[c]	–[c]	–[c]	–[c]	–	155.1	132.9	99.9	167.3
24[b]		5.2	3.7	≤ 1.3	≤ 1.3	$^{3}J(1,HN) = 7.8$ $^{2}J(2,HN) \leq 1.3$	155.6	138.3	88.6	168.3
25[b]		5.4	3.8	≤ 1.3	1.3	$^{3}J(2,HN) = 6.0$ $^{2}J(1,HN) \leq 1.3$	154.1	141.0	113.8	165.8
26[b]		6.0	*ca.* 3.5	≤ 1.3	≤ 1.3	$^{3}J(2,HN) = 5.8$ $^{2}J(1,HN) \leq 1.3$	154.2	140.9	114.1	165.4
27		3.7	3.7	2.5	≤ 1.3	–	153.8	144.9	105.8	163.3

[a] $^{3}J(1,H-C(3)) = {}^{3}J(C(1),H-C(3))$. [b] In (CD$_3$)$_2$SO. [c] Not determined.

A more crucial point is the controversy whether the structure of the thiourea-acetylenedicarboxylate addition product is of type I or type II (see *Scheme 1* and *3*). To distinguish between these two constitutional isomers C,H-spin-coupling constants of the carbonyl C-atoms with the vinyl proton can be used. In the case of **1**, whose structure has been determined by X-ray analysis [14], the lactam-carbonyl exhibits a coupling of 5.3 Hz with the vinyl proton H–C(3) ($^3J(1, H{-}C(3))$), whereas the ester-carbonyl couples with only 1.2 Hz with the same proton ($^2J(4, H{-}C(3))$; *Table 1*). The assignment of the two carbonyl resonances is discussed below.

Scheme 3[2])

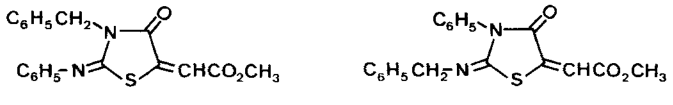


1 (I) (II)

Similarly, the product **8** of the condensation of 2-methylimino-3-methyl-1,3-thiazolidin-4-one with benzaldehyde [18] exhibits a 6.4 Hz coupling constant of the lactam carbonyl with H–C(3) ($^3J(1, H{-}C(3))$), in agreement with the expected five-membered structure of type I. The alternative compound **18** of type II was obtained from the reaction of *N,N*-dimethylthiourea with phenylpropiolic ester [19]. In this case, the lactam carbonyl shows a small and non-resolved coupling with the vinyl proton ($^2J(1, H{-}C(2)) \leq 1.3$ Hz). An analogous behaviour is observed for the isomeric pair **9** [20] and **19** [19]. The large vicinal C,H-coupling ($^3J(4, H{-}C(2))$) of the ester carbonyl in structures of type II is observed in **16** and **17** *(Table 2)*. Thus, the difference between vicinal and geminal C,H-coupling constants (^2J and ^3J, respectively) can serve, in the present series of compounds, as a criterion to differentiate between I and II. Thiazolidinone rather than dihydrothiazinone structures are similarly established for **2**–**7** [4].

When unsymmetrically substituted thioureas are used in the condensation reaction, a further possibility for constitutional isomerism exists, as illustrated in the case of the addition product **2** (see *Scheme 4*). The two structures for **2**, Ia and Ib, can readily be distinguished by the multiplicity of the proton coupled amide-carbonyl resonance. There are two signals for **2** in the relevant chemical shift range (160–170 ppm). One appears at 165.9 ppm as a quartet (3.7 Hz) with doublet fine structure (≤ 1.3 Hz) as expected for the ester carbonyl C-atom of both Ia and Ib. The other resonance is a doublet (5.0 Hz) at 164.4 ppm with an additional triplet

Scheme 4

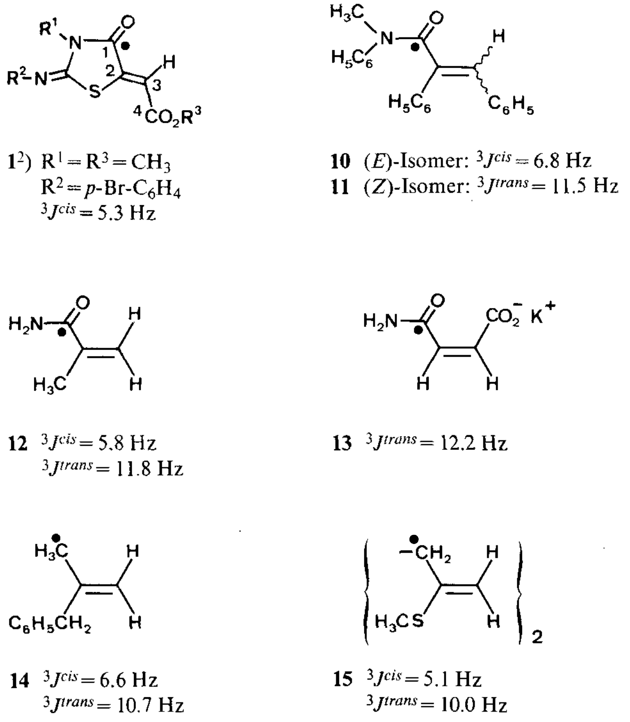


2 (Ia) (Ib)

splitting (3.9 Hz). This coupling pattern originates from spin interaction of the lactam carbonyl C-atom C(1) with the vinyl proton H–C(3) and the *N*-benzyl protons, respectively. The magnitude of the latter coupling constant agrees well with a vicinal C(1)–NCH_2 arrangement as present in Ia and clearly rules out Ib in which the coupled nuclei would be separated by five bonds. This confirms earlier chemical results [10]. Similar coupling constants are observed for the thiazolidinones **1**, **4** and **8**. Assignment of the lactam- and ester-carbonyl resonances is always possible on the basis of signal multiplicities except in the case of **1**. Here, chemical shift correlation with compounds **2-4**, as well as the relative magnitudes of the vicinal coupling C(1),*H*–C(3) and the geminal coupling C(4),*H*–C(3) *(Table 1)* can be used.

We now turn our attention to the geometry of the double bond in compounds of type I (*i.e.* **1-9**). The crucial parameter for an assignment of the configuration of the C(2),C(3) double bond by NMR. is given by the *vicinal* coupling constant between the lactam carbonyl C-atom C(1) and the olefinic H-atom at C(3). The value of 5.3 Hz observed for **1** is in good agreement with $^3J^{cis}_{(C,H)}$ of the reference compounds **10** [16] and **12**, whereas $^3J^{trans}_{(C,H)}$ of **11** [16], **12** and **13** [16] is roughly twice as large *(Scheme 5)*.

Scheme 5[a])



1[2]) $R^1 = R^3 = CH_3$
$R^2 = p\text{-Br-}C_6H_4$
$^3J^{cis} = 5.3$ Hz

10 (*E*)-Isomer: $^3J^{cis} = 6.8$ Hz
11 (*Z*)-Isomer: $^3J^{trans} = 11.5$ Hz

12 $^3J^{cis} = 5.8$ Hz
$^3J^{trans} = 11.8$ Hz

13 $^3J^{trans} = 12.2$ Hz

14 $^3J^{cis} = 6.6$ Hz
$^3J^{trans} = 10.7$ Hz

15 $^3J^{cis} = 5.1$ Hz
$^3J^{trans} = 10.0$ Hz

[a]) The vicinal coupling counterpart of the olefinic H-atom is the dotted C-atom.

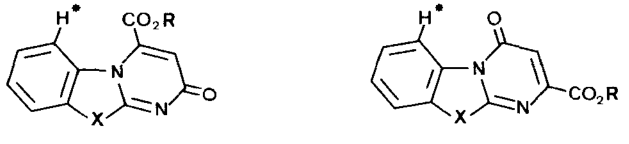
Incorporation of the coupled carbonyl (dotted C-atom) in a five-membered heterocycle does not exert a large influence on the *cis* and *trans* C, H-coupling constants as it was shown for an (*E*, *Z*) pair of structurally related γ-lactones [15]. Furthermore, substitution of a C-atom attached to the double bond by a S-atom results in only a slight decrease of $^3J^{cis}_{(C,H)}$ and $^3J^{trans}_{(C,H)}$, *cf.* **14** and **15**.

Thus, the observed value of 5.3 Hz for $^3J_{(C,H)}$ of **1** closely corresponds to the expected value of a trisubstituted C, C-double bond with the given substitution pattern. The range of 4.8-6.4 Hz obtained for $^3J(1, H{-}C(3))$ of **1-5** and **7-9** clearly demonstrates that all these compounds possess (*Z*)-configuration of the double bond *(Table 1)*. Compound **6** which has a different electronic structure in the five-membered ring (extended conjugation) exhibits an exceptionally low value (3.6 Hz) for $^3J^{cis}_{(C,H)}$. The structure of **6**, however, has been determined by X-ray analysis [13].

It is interesting to note that 'conventional' data like IR., UV., ^{1}H-NMR. and mass spectral data do not provide conclusive answers to this configurational problem; in fact, mass spectral fragmentation analysis led earlier workers to wrong conclusions [6].

In contrast to the thiourea-acetylenedicarboxylate addition products, those arising from 2-aminobenzothiazole and 2-aminobenzimidazole have the six-membered pyrimidine structures **16** and **17**, respectively. Structure **16** has been derived earlier by MS. and ^{1}H-NMR. studies [21] and confirmed recently by X-ray analysis [22]. The skeleton of **17** follows from the X-ray analysis of the *N*-methyl-2,3-dihydro derivative [23]. Our studies confirm these observations. The ester carbonyl C-atom C(4) (identified by its coupling to the methyl protons) exhibits a rather large interaction with H−C(2) (4.2-4.3 Hz) whereas the amide carbonyl is coupled by only ≤1.0 Hz to the same proton. Thus, the coupling behaviour of the two carbonyl C-atoms with the olefinic proton is just opposite to the one observed for compounds **1-9** of *Table 1*. It must be pointed out that ^{13}C-NMR. spectroscopy cannot easily distinguish between structures of type VI and VII *(Scheme 6)*. ^{1}H-NMR. spectra, however, help to rule out VII in favour of VI for **16** and **17** since the starred proton does not show the deshielding effect due to the lactam carbonyl [21] [23] as expected for structure VII.

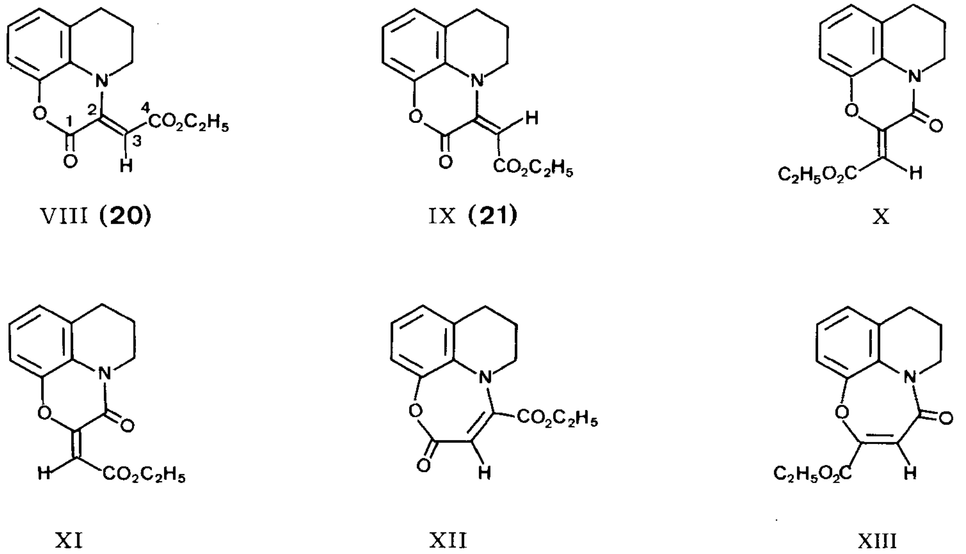
Scheme 6



VI VII

We will now discuss another series of adducts obtained from the reaction of acetylenedicarboxylates with 1,2-difunctionalized aromatic systems *(Table 3)*. As an example, the different structural isomers VIII-XIII will be considered which can be expected for the two products of the reaction of 8-hydroxytetrahydroquinoline

Scheme 7[2])

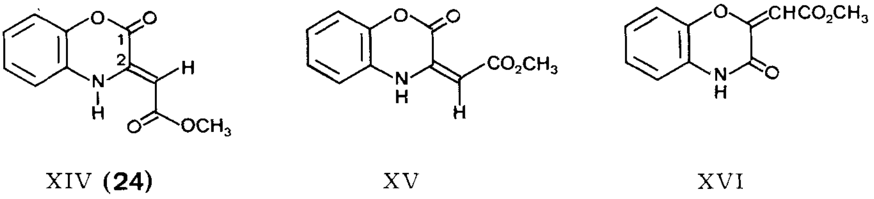


VIII **(20)** IX **(21)** X

XI XII XIII

with diethyl acetylenedicarboxylate [24]. Since in the proton-coupled ^{13}C-spectrum of the mixture the ring carbonyl resonances are clearly identified (doublets, no further spin coupling to CH_2N protons), the six-membered lactam structures X and XI can be ruled out. In our earlier study [24] the argument against X and XI was the presence of a band in the IR. spectrum at 1740 cm^{-1} and at 1780 cm^{-1} in the dihydro derivative. ^1H-NMR. [24] and ^{13}C-NMR. spectra indicate slow equilibration of the two products from a 1:4 to a 3:2 ratio in DMSO-d_6 solution. The two isomers differ in the coupling constant of the ring carbonyl with the vinyl proton (5.6 and 11.3 Hz, respectively). These data indicate the existence of (*E*, *Z*) isomerism at an exocyclic double bond and, in addition, the ready equilibration excludes structural alternatives with a seven-membered lactone XII or lactam XIII. Hence, the two isomers **20** and **21** have the structures VIII and IX. The corresponding methyl ester similarly exists as a mixture of **22** and **23** *(Table 3)*. The product **24** obtained from 2-aminophenol and dimethyl acetylenedicarboxylate has been established [25] to have the lactone structure XIV. The stereoisomeric lactone

Scheme 8[2])



XIV **(24)** XV XVI

structure XV and lactam structure XVI were ruled out for chemical and spectroscopic reasons. In the ^{13}C-NMR. spectrum of **24** C(1) shows a large coupling constant with H—N ($^3J^{trans} = 7.8$ Hz) confirming structure XIV. Further, the coupling between C(2) and H—N cannot be resolved ($^2J \leqslant 1.3$ Hz). In the alternative lactam structure XVI, the 7.8 Hz coupling would have to be assigned to the geminal C(1), H—N interaction and the small, unresolvable coupling to the *trans* vicinal C(2), H—N interaction, which is unreasonable [26]. The (*Z*)-configuration of the C,C-double bond is confirmed by the value $^3J(\mathrm{C}(1), H\text{—}\mathrm{C}(3)) = 5.2$ Hz. The assignment of the two coupling constants of C(1) was established by selective decoupling experiments.

The above mentioned lactam structure XVI is realized in the products **25** and **26** from the reaction of 2-aminothiophenol with dimethyl and diethyl acetylenedicarboxylate, respectively. Earlier chemical work had established the lactam structures unambiguously [27], but the configuration of the double bond was left uncertain. In these cases C(1) does not show a resolvable coupling with H—N despite the slow proton exchange in DMSO solution, instead C(2) is coupled to H—N ($^3J^{trans} = 5.8$-6.0 Hz). The (*Z*)-configuration at the exocyclic double bond again follows from the magnitude of $^3J(\mathrm{C}(1), H\text{—}\mathrm{C}(3))$ (5.4 and 6.0 Hz respectively).

The benzodioxane derivative **27** obtained from the rearrangement of the addition product of catechol and dimethyl acetylenedicarboxylate [28] has also (*Z*)-configuration at the exocyclic double bond. The significantly lower value for $^3J(\mathrm{C}(1), H\text{—}\mathrm{C}(3))$ in **27** agrees with data observed in other enolic systems [15].

In conclusion, the present study demonstrates that C,H-coupling constants are a powerful and widely applicable tool in unravelling gross and fine details of structures of heterocyclic products obtained from heteronucleophiles and acetylenedicarboxylates.

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Experimental part. - The synthesis of all compounds is described in the literature, for ref. see above. Compound **14** is of commercial origin *(Fluka AG)* and **15** was kindly supplied by Dr. *W. Rieder*, Org.-chem. Inst., Universität Wien. ^{1}H-NMR. spectra were measured on a *Varian* HA-100 spectrometer and ^{13}C-NMR. spectra on a *Varian* XL-100-12 spectrometer in 10 mm sample tubes with TMS as an internal standard. The latter instrument was equipped with a PFT unit and a 620L 16K computer. Proton-coupled ^{13}C-NMR. spectra were measured using spectral widths of 5000 or 2500 Hz and acquisition times of 0.8 and 1.6 s, respectively, corresponding to digital resolutions of 1.3 Hz or 0.7 Hz. The reproducibility of C,H-coupling constants measured under these conditions is better than ± 0.5 Hz. Reduced splittings obtained from selective decoupling experiments were corrected as described in [15] using the exact formula for J_r derived by *Anderson & Freeman* [29] and by *Ernst* [30]. Where the solubility of a compound was too low, spectra could be obtained a V-4418 probe utilizing 18 mm sample tubes. $CDCl_3$, DMSO-d_6 and $CDCl_3$/DMSO-d_6 1:1 were used and concentrations varied from 0.03M to 1M.

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