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Ritter Reactions. XII. Reappraisal of the Reactivity of Methyl Schiff Bases with Dimethyl Acetylenedicarboxylate

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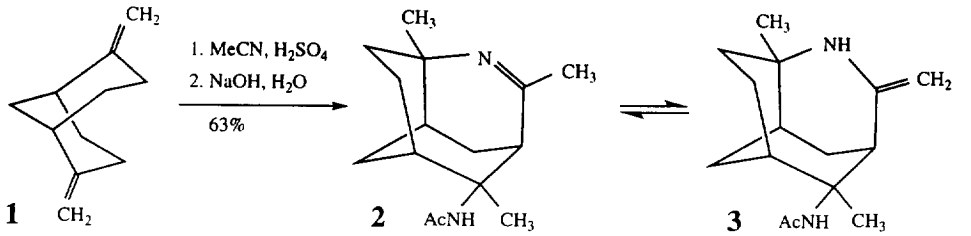
Abstract: The reaction of the methyl Schiff base compound **2** with dimethyl acetylenedicarboxylate (DMAD) has been reinvestigated in order to determine whether it is initiated through the imine form **2** or the enamine tautomer **3**. The structure of the reported 1:1 adduct is reassigned as **6** following elucidation by a combination of NMR techniques including natural abundance gradient enhanced ^{1}H-^{15}N HMBC and 1D HSQC, as well as ^{1}H, ^{13}C, DEPT, DQF-COSY, NOESY, ^{1}H-^{13}C HMQC and HMBC. Similar experiments, plus ^{13}C-^{13}C INADEQUATE data, for the 1:1 adduct of imine **10** and DMAD require its reassignment as structure **15**. $^{3}J_{NH}$ values were used as an indicator of the likely geometries of these products. In both cases, the products are the eventual outcome of initial attack on DMAD by the nitrogen of the imine form. © 1997 Elsevier Science Ltd.

INTRODUCTION

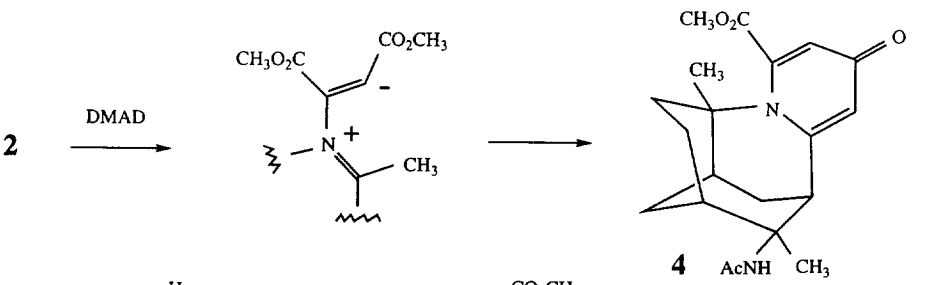
Reaction of 2,6-bis(methylene)bicyclo[3.3.1]nonane **1** with acetonitrile and sulfuric acid affords the tricyclic methyl Schiff base product **2** in good yield as its monohydrate.[1,2] This one-flask process first of all involves transannular addition of the azenometheno bridge through the intramolecular variant[3] of the Ritter reaction. The resulting carbenium ion intermediate is then trapped by a second equivalent of acetonitrile to yield the acetamido group by means of the more conventional type of Ritter reaction.[4,5]

Methyl Schiff bases such as this product are potential ambident nucleophiles capable of reacting either through the imine form **2** or the alternative enamine tautomer **3**. They also are reactive towards dimethyl acetylenedicarboxylate (DMAD), with which they are known to yield a wide variety of different product types.[6-8] Unfortunately the exact outcome of any given case is highly unpredictable and therefore structural assignments require careful consideration.[9] Consequently, during our investigations of the reactivity of cyclic imines with DMAD, we prefer to confirm product structures using X-ray crystallography whenever possible.[10,11]

Earlier we reported that (**2**)·H_2O gave a 48% yield of an orange adduct $C_{20}H_{26}N_2O_4$ when refluxed with DMAD in chloroform.[10] The molecular formula indicated addition of one equivalent of DMAD together with cyclisation and loss of methanol. Likely isomeric structures would be compounds **4-6** if the reaction took place through the imine tautomer **2**, and **7-9** if it had been initiated by the enamine form **3**. Unfortunately, crystalline samples of the product grown from a variety of solvents suffered from twinning disorder which



1 **2** **3**



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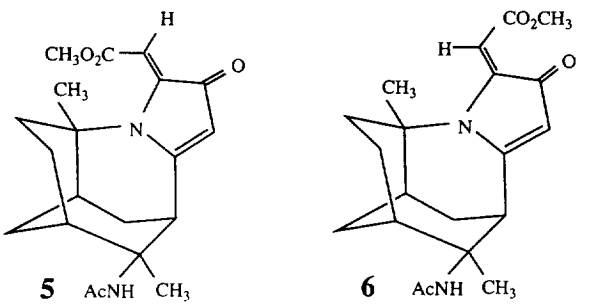
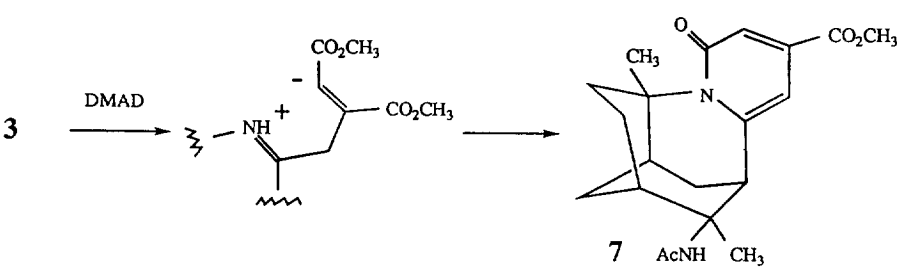


5 **6**



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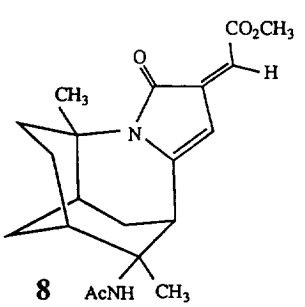

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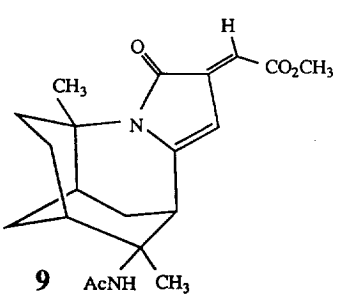

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prevented X-ray structure determination.[12] By analogy with a previous report,[13] we proposed the six-membered ring lactam structure **7** for this material.[10] However, in light of the capricious nature of such DMAD reactions, we became increasingly uneasy with this structural assignment to the extent of carrying out the reinvestigation reported here using NMR spectroscopic methods.

RESULTS AND DISCUSSION

Structure of the 1:1 adduct of 2 *with DMAD*

The ^{13}C and DEPT spectra of the 1:1 DMAD adduct revealed the correct number and multiplicities of carbons for this type of structure. Assignment of the carbons and protons of the tricyclic core, present in the starting material **2** before the reaction with DMAD, follows from the routine analysis of the DQF-COSY, HSQC and HMBC spectra. The nature of the product resulting from the DMAD condensation is inferred as structure **6** primarily from the ^{13}C HMBC spectrum. Figure 1 shows the structure of **6** and the atomic labelling scheme used in this work, where carbons are designated as letters A-T, nitrogen atoms as α and β, and the non-equivalent protons as numerals 1-18. The chemical shift values for these atoms are listed in Table 1.

The main region of interest in the ^{13}C HMBC spectrum is shown in Figure 2. Intense crosspeaks between H9 and carbon S (not shown in Figure 2), H15 and carbon S and carbon N (which bears H16), and between H16 and carbon S and carbon I (not shown) confirm the positions of the quaternary carbon S and the protonated carbon N. Hydrogen atom H16 also shows intense crosspeaks to quaternary carbons T and P, suggesting that these are both two or three bonds from H16 which argues against structures **4** and **7**. However, there is no cross peak between H16 and the other protonated carbon indicative of them being more than three bonds apart. In any of the other structures **4**,**7-9**, a relatively large $^3J_{CH}$ coupling constant between H16 and carbon N would be expected, leading to an intense cross peak in the spectrum. Hydrogen atom H18 shows strong correlations to carbons P and T and a low intensity correlation to carbon Q, again consistent with structure **6**. H18 does show a correlation to carbon N but the size of the coupling responsible (<2 Hz) is more consistent with a four-bond interaction. Indeed, a feature of the gradient enhanced (ge) HMBC spectra of **6** (and also DMAD adduct **15**) is the large number of visible low intensity cross peaks which are the result of four- or even five-bond couplings.

Strong evidence for the (*E*)-isomer of the exocyclic double bond being present (*i.e.* **6** rather than **5**) is obtained from the NOESY spectrum. Relatively strong cross peaks are observed between H18 and H10 and especially to the methyl protons H4 indicative of their spatial proximity. Molecular modeling studies showed that the distance between H18 and the centroid of the H4 methyl protons in low energy conformations of each isomer was 2.5-2.9 Å in the (*E*)-isomer **6** and around 4.4-4.5 Å in the (*Z*)-isomer **5**. Indeed, this observation on its own provides strong evidence that this assignment is correct since no other structure would create this spatial proximity.

A further possibility for determining the stereochemistry around this bond is to measure $^3J_{NH}$ and/or $^3J_{CH}$ values. The use of gradients now allows routine acquisition of ^1H-^{15}N HMBC or long range HSQC spectra at natural abundance of ^{15}N.[14] Expansions of the normal proton, 1D ^1H-^{15}N ge-HSQC, and ^1H-^{15}N ge-HMBC spectra of **6** are shown in Figure 3. The correlations observed in the HMBC spectrum, notably from protons H18, H16 and H4 to Nα help confirm the assigned structure. The separations of the antiphase lines in

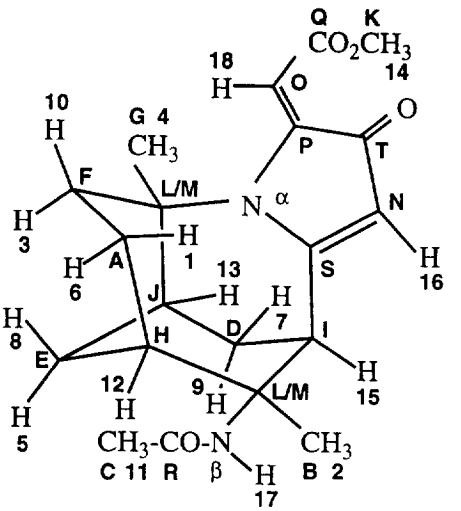


Figure 1. Structure **6** showing the atom coding used in the NMR analyses.

Table 1. NMR chemical shift assignments (ppm) for structure **6** (see Figure 1):

Proton	Shift	Carbon	Shift	Nitrogen	Shift
1	1.26 (m)	A	19.4	α	-256
2	1.46 (s)	B	21.8	β	-248
3	1.56 (m)	C	24.8		
4	1.58 (s)	D	25.5		
5	1.66 (m)	E	25.9		
6	1.68 (m)	F	29.4		
7	1.74 (m)	G	29.6		
8	1.81 (m)	H	36.1		
9	1.84 (m)	I	36.5		
10	1.93 (dd)	J	37.5		
11	1.98 (s)	K	52.7		
12	1.99 (m)	L	59.7		
13	2.06 (m)	M	59.8		
14	3.82 (s)	N	99.9		
15	3.97 (m)	O	107.9		
16	5.12 (s)	P	138.9		
17	5.53 (br s)	Q	167.5		
18	5.85 (s)	R	169.9		
		S	176.6		
		T	184.5		

the 1D HSQC spectrum reveal the couplings of H16 and H18 to Nα. While there is insufficient literature data available for an unequivocal assignment of (*E*)- or (*Z*)-isomers, the observed $^{3}J_{N\alpha\text{-}H18}$ value of 1.8 ± 0.2 Hz is more consistent with a *cis* H-N coupling constant and hence the (*E*)-isomer.[15] This *J* value is noticably smaller than that between the *trans*-related H16 and Nα, $^{3}J_{N\alpha\text{-}H16}$ = 3.5 ± 0.2 Hz. Spectra of **6** show evidence for the presence of a second isomer in lower concentrations (5-10%). The presence of a singlet resonance at δ 6.16 with a coupling to ^{15}N of *ca.* 5.1 Hz suggests this minor species may be the (*Z*)-isomer **5**, this proton being from the proton equivalent to H18 in the major product.

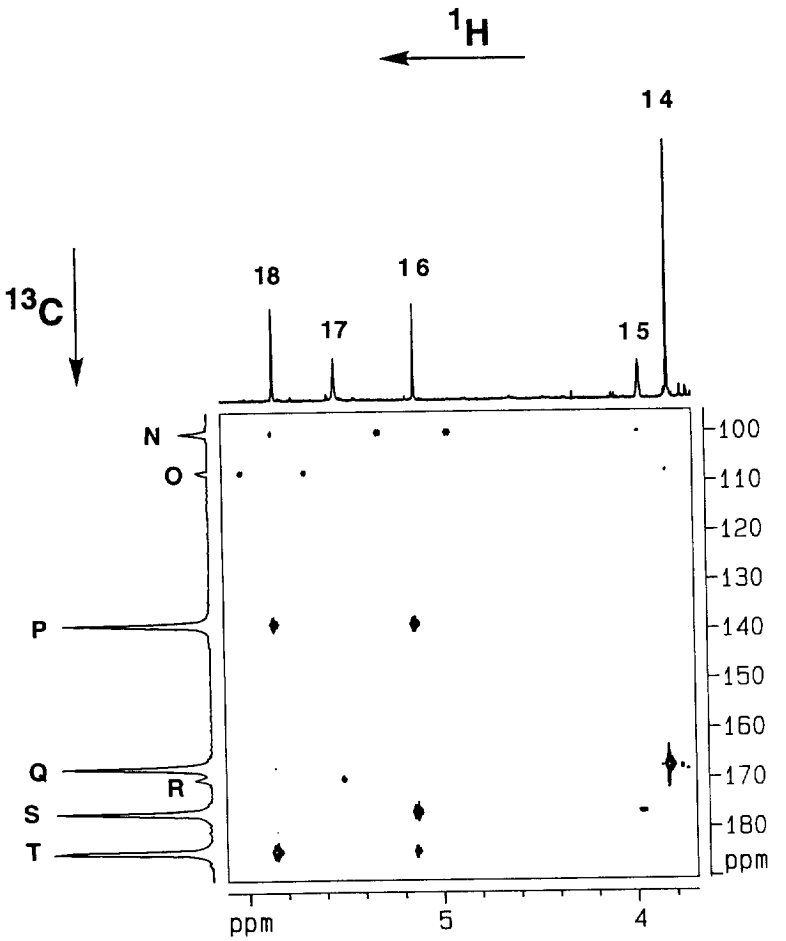


Figure 2. Expansion of the ^{1}H-^{13}C HMBC spectrum of **6**, annotated with the normal ^{1}H spectrum in F_2 and partial ^{13}C projection in F_1.

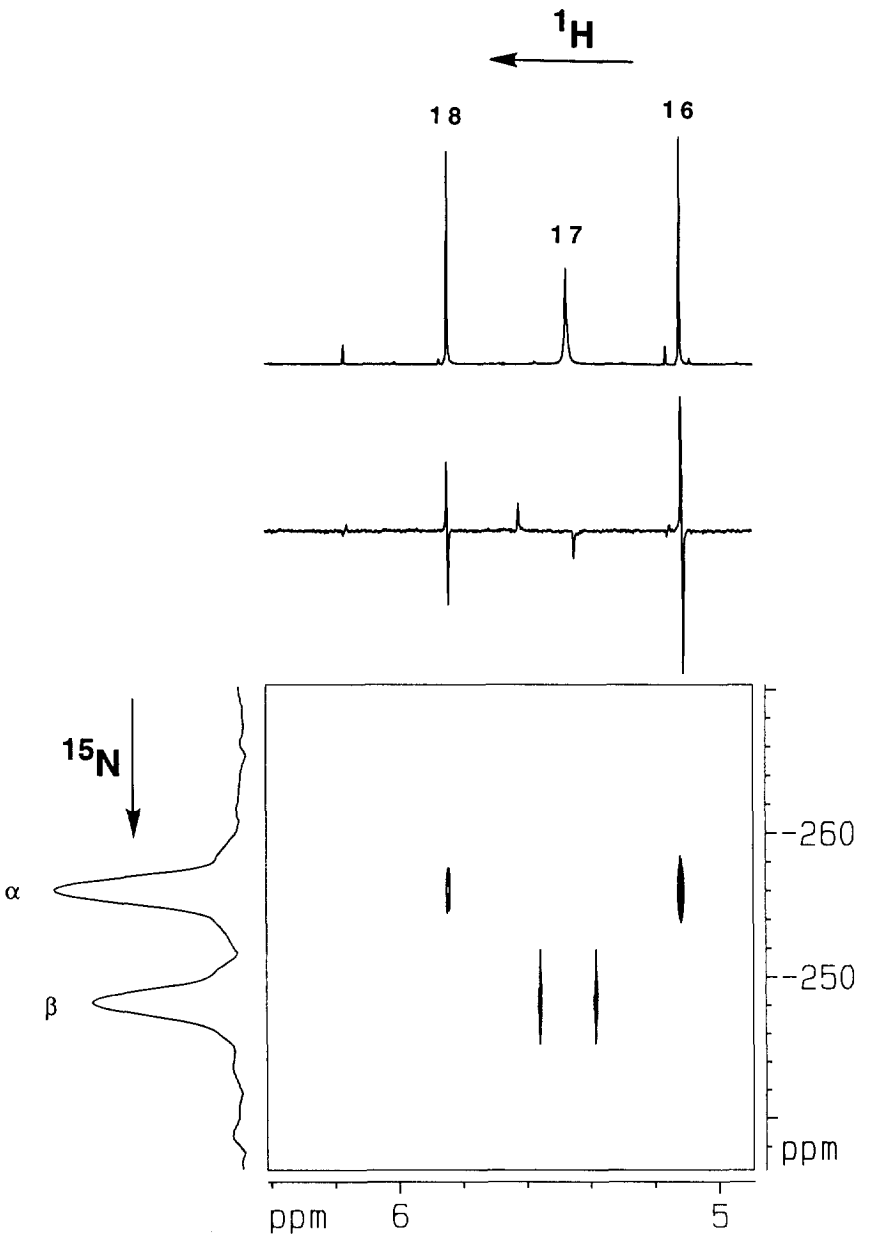


Figure 3. Expansions of NMR spectra of compound **6**:

Top: normal 1D spectrum;

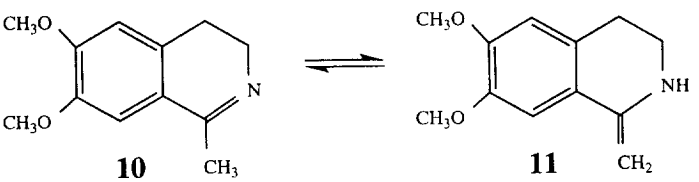
Middle: 1D ^{1}H-^{15}N HSQC spectrum showing antiphase lines separated by $^nJ_{NH}$;

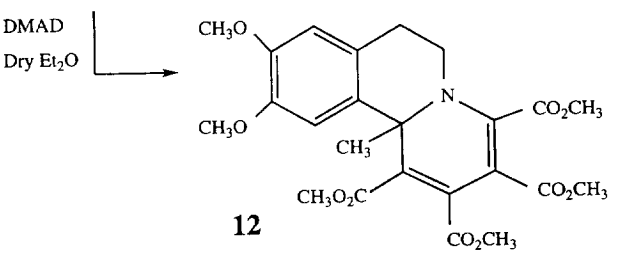
Bottom: ^{1}H-^{15}N HMBC spectrum with ^{15}N projection in F_1.

Reactions of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline 10 with DMAD

The structure of the 1:1 adduct of **2** and DMAD was originally assigned through analogy with the behaviour of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **10**. This compound is reported to yield two quite different DMAD addition products depending on the reaction conditions employed. From dry diethyl ether the 1:2 adduct **12** is obtained, while from methanol a bright red 1:1 adduct is formed.[13] In light of the above results we decided to examine both these products further.

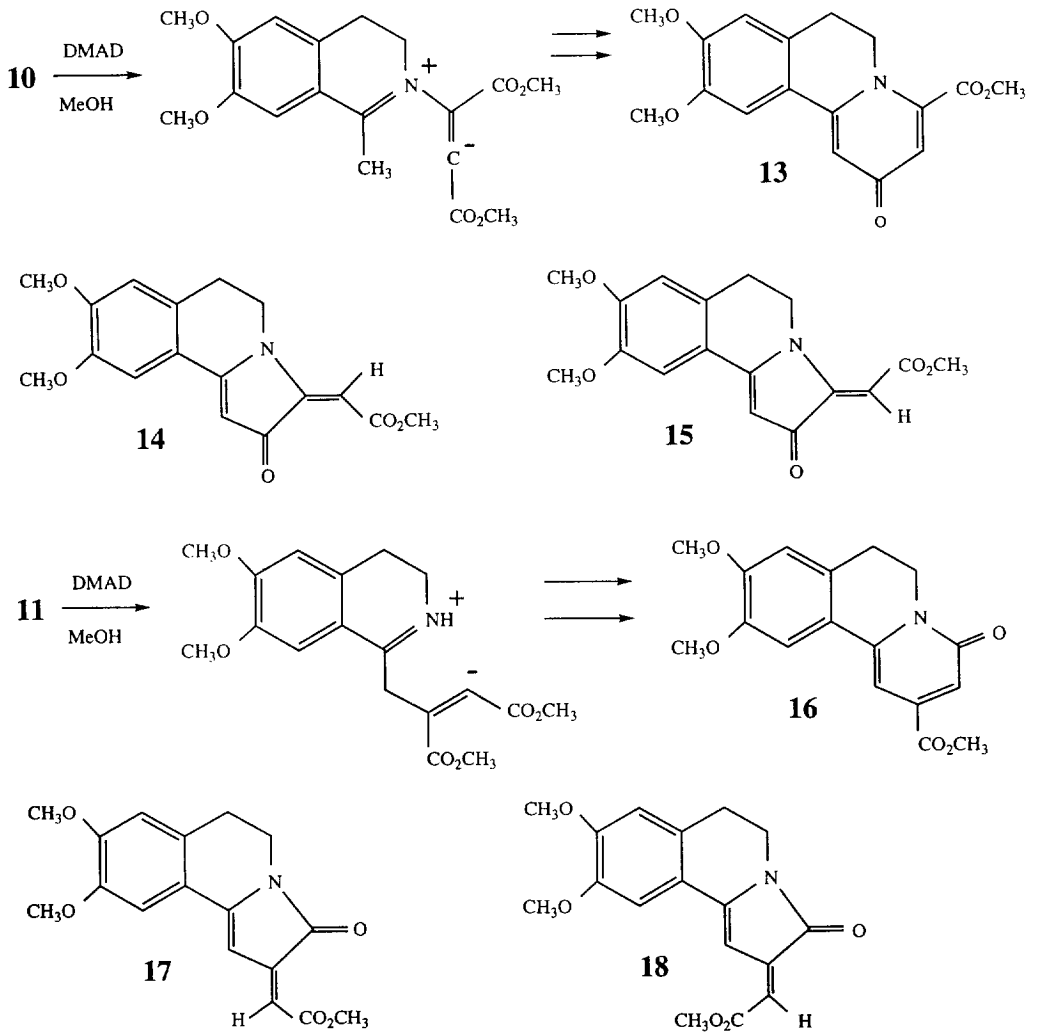
First of all, **10**[16] was reacted with DMAD in anhydrous diethyl ether as described by Nair[13] to obtain the reported 1:2 adduct. Microanalysis confirmed the formula as being $C_{24}H_{27}NO_{10}$ which corresponds to addition of two DMAD molecules and formation of a third ring. The mass ion M^+ was not observed by EI MS but a prominent peak at 474 corresponding to $(M-15)^+$ was recorded. Both the ^1H and ^{13}C NMR spectra clearly showed the six methoxy groups anticipated for the structure and, most importantly, a seventh methyl group at δ_H 1.68 and δ_C 22.1 ppm corresponding to the angular aliphatic methyl group. Hence there is little doubt that the proposed structure **12** is correct, particularly since corresponding cyclic tetraesters have been obtained in many related cases.[17-19]





Secondly, the imine **10** was reacted with DMAD in methanol as described[13] to produce the reported 1:1 adduct. In this reaction only one molecule of DMAD reacts but formation of the new heterocyclic ring also involves loss of a molecule of methanol. The m.p. of our product was lower than the literature value, but from comparison with its published ^1H NMR spectrum it was clearly the same compound. In addition the microanalysis and mass ion data fully supported the expected formula $C_{17}H_{17}NO_5$. This product was recrystallised from benzene yielding needle-like crystals. X-Ray diffraction data was recorded for one such crystal without any indication of difficulty but, unfortunately, this structural data could not be solved by direct methods (MULTAN80).[12]

Unlike compound **12** no angular aliphatic methyl group is present in this product as indicated by ^{1}H and ^{13}C NMR spectroscopy. Therefore six probable structures need to be considered on mechanistic grounds. If the process commences by initial attack using the nitrogen atom of the imine form **10**, then the vinylogous lactams **13-15** could result. Conversely, if it commences through the enamine tautomer **11**, then the isomeric lactams **16-18** could be produced. The original report[13] considered possibilities **13,16-18** and selected **16** through arguments based on IR and ^{1}H NMR spectral measurements.



Structure of the 1:1 adduct of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline* 10 *and DMAD

A similar strategy of using HSQC and HMBC as for the determination of **6** revealed that the 1:1 DMAD adduct had the structure **15**. While the reaction leading to this compound had been performed before, its

structure therefore turned out to be different to that proposed earlier and even to any of those previously considered.[13]

In view of this, a 2D INADEQUATE experiment was performed which confirmed the assignments of all the carbons in its ^{13}C skeleton. Figure 4 shows the structure of **15** with the atomic labelling scheme used, where carbons are designated as letters A-Q, the nitrogen atom α, and the non-equivalent protons as numerals 1-9. Table 2 lists the chemical shift values determined for these atoms.

The compound was a similar cyclisation product to **6**, but experiments this time indicated the presence of the (*Z*)-isomer. Irradiation of the methylene protons H5 in a steady state NOE experiment gives only a small enhancement (2%), which appears more consistent with interproton distances of 4.0 - 4.6 Å found in the (*Z*)-isomer **15** rather than the short distances of 2.1-3.0 Å predicted in models of the (*E*)-isomer **14**. The T_1 of the H7 proton is long (*ca.* 3.8 s) which also suggests its spatial isolation. Again, measurement of $^3J_{NH}$ involving H7 gives stereochemical information. The value of 4.8 Hz extracted from the natural abundance ^1H-^{15}N HMBC spectrum suggests a *trans*-coupling and hence the (*Z*)-isomer.[15] Similarly, the $^3J_{CH}$ value of 4.8 Hz from the ^1H-^{13}C HMBC spectrum indicates a *cis*-coupling.[20]

Table 2. NMR chemical shift assignments (ppm) for structure **15** (see Figure 4):

Proton	Shift	Carbon	Shift
1	3.04 (t)	A	28.4
2	3.76 (s)	B	42.3
3	3.90 (s)	C	51.9
4	3.94 (s)	D	56.1
5	4.28 (t)	E	56.1
6	5.68 (s)	F	94.4
7	6.00 (s)	G	98.4
8	6.74 (s)	H	109.8
9	7.06 (s)	I	110.7
		J	117.1
		K	131.2
Nitrogen	**Shift**	L	143.4
α	-270	M	148.4
		N	153.2
		O	166.1
		P	166.5
		Q	187.0

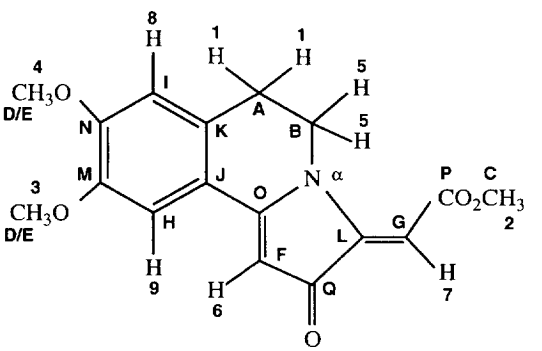
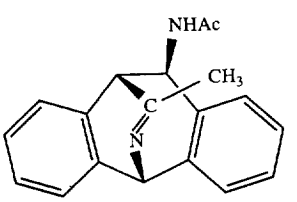


Figure 4. Structure **15** showing the atom coding used in the NMR analyses.



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Conclusions

These results therefore demonstrate that the compounds whose structures are reported in the literature as being **7** and **16** are both incorrectly assigned. These are really **6** and **15** respectively. Under the conditions used in these experiments all three imine-DMAD products **6**, **12**, **15** arose after initial attack by the nitrogen atom of the imine tautomer, rather than by the carbon of the enamine tautomer. In other work we have noted similar behaviour for the heterocyclic system **19**.[11] However, we have also observed that this initial product can undergo reaction with a second equivalent of DMAD through its enamine tautomer.[11] Furthermore, we have demonstrated that the hydrogen atoms of the imine methyl group of **2** undergo efficient exchange *via* the enamine form using D_2O.[1,2] Therefore the above structural reassignments do not necessarily preclude the enamine tautomer from initiating reactions with DMAD in different compounds or circumstances. Hence particular caution should be applied when assigning structures to materials produced in such methyl Schiff base-DMAD reactions.

EXPERIMENTAL

Preparative work

Melting points were recorded using a Kofler instrument and are uncorrected. The IR spectra were recorded on a Hitachi 260-10 spectrometer and significant peaks are labelled as strong (s), medium (m), or weak (w). For the preparative work ^1H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded using a Bruker ACF300 instrument and are listed as chemical shifts δ relative to $SiMe_4$. The substitution of carbon atoms was determined using the DEPT procedure. Mass spectra were determined using a VG Quattro triple quadrupole instrument by Dr. J.J. Brophy, and elemental analyses were carried out at UNSW by Dr. H.P. Pham.

(3α,4aβ,6α,8aβ,9R)-*N*-(2,8a,9-Trimethyl-3,4,4a,5,6,7,8,8a-octahydro-3,6-methanoquinolin-9-yl)-acetamide* **2** *monohydrate*

The monohydrate form of imine **2** was prepared from 2,6-bis(methylene)bicyclo[3.3.1]nonane **1**, acetonitrile, and sulfuric acid as described previously.[1,2]

Methyl (E)-{exo-*11-acetylamino-9a,*endo-*11-dimethyl-2-oxo-4,5,5a,6,7,8,9,9a-octahydro-4,7-methano-pyrrolo[1,2-*a*]quinolin-1-ylidene}-2-ethanoate* **6**

This material was prepared from **2** monohydrate and DMAD in refluxing chloroform as described previously[10] except that column chromatography on silica using ethyl acetate-ethanol (9:1) was used to separate the product from tarry impurities. The crude material was then recrystallised from ethyl acetate to afford **6**.

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline **10**

The imine **10** was prepared by the method of Brossi *et al.*,[16] m.p. 105-107 °C; lit.[16] 105-107 °C. ^{13}C NMR δ ($CDCl_3$) 164.5 (C), 151.3 (C), 147.5 (C), 131.2 (C), 121.9 (C), 110.2 (CH), 109.1 (CH), 56.1 (CH_3), 55.9 (CH_3), 46.2 (CH_2), 25.6 (CH_2), 22.9 (CH_3).

Tetramethyl 9,10-dimethoxy-11b-methyl-7,11b-dihydro-6H-benzo[a]*quinolizine-1,2,3,4-tetracarboxylate* **12**

Imine **10** (3.08 g, 15 mmol) was dissolved in dry ether (70 mL) and DMAD (4.26 g, 30 mmol) in dry ether (10 mL) added with stirring at 0 °C. After 15 min a small amount of tarry material had precipitated leaving a brown solution. The cooling bath was removed and the vigorously stirred mixture was allowed to warm to room temperature. The product then commenced precipitating as a sandy coloured solid. After 5 h this was filtered and recrystallised from methanol to give the tetraester **12** as a pale yellow solid. Yield (1.70 g, 23%), lit.[13] 18%. M.p. 186-188 °C; lit.[13] 187 °C. (Found: C, 59.03; H, 5.70; N, 2.67. $C_{24}H_{27}NO_{10}$ requires C, 58.89; H, 5.56; N, 2.86%). ν_{max} (paraffin mull) 1720s, 1680s, 1600s, 1510s, 1340s, 1310m, 1250s, 1200s, 1120s, 1150m, 1060w, 1010w, 960m, 880m, 820m, 750m cm^{-1}. ^1H NMR δ ($CDCl_3$) 6.91 (s, 1H), 6.53 (s, 1H), 3.90 (s, 3H), 3.81 (s, 6H), 3.67 (s, 3H), 3.63 (s, 3H), 3.50 (m, 1H), 3.41 (m, 1H), 3.35 (s, 3H), 2.94 (m, 1H), 2.60 (m, 1H), 1.68 (s, 3H). ^{13}C NMR δ ($CDCl_3$) 167.0 (C), 165.6 (C), 164.6 (C), 164.3 (C), 148.5 (C), 148.2 (C), 147.4 (C), 129.8 (C), 127.4 (C), 126.9 (C), 123.9 (C), 111.2 (CH), 111.0 (CH), 98.8 (C), 60.9 (C), 55.9 (CH_3), 55.7 (CH_3), 53.2 (CH_3), 52.2 (CH_3), 51.9 (CH_3), 51.4 (CH_3), 45.7 (CH_2), 29.7 (CH_2), 22.1 (CH_3). *m/z* 474 (M-15, 7%), 85 (82), 83 (100), 48 (46), 47 (92).

Methyl (Z)-{8,9-dimethoxy-2-oxo-5,6-dihydropyrrolo[2,1-a]isoquinolin-3-ylidene}-2-ethanoate **15**

To a solution of imine **10** (5.15 g, 0.025 mol) in methanol (100 mL), a solution of DMAD (5 mL) in methanol (20 mL) was added dropwise. After 3 hours at room temperature, the bright red solid **15** was filtered and washed with a little methanol. Yield (6.00 g, 76%), (lit.[13] 78%). M.p. 211-212 °C (decomp.; from CH_2Cl_2 containing a little CH_3OH), lit.[13] 226-228 °C. (Found: C, 64.58 ; H, 5.70; N, 4.16. $C_{17}H_{17}NO_5$ requires C, 64.75; H, 5.43; N, 4.44%). ν_{max} (paraffin mull) 1715s, 1670s, 1640s, 1610w, 1580s, 1505m, 1340s, 1320m, 1290m, 1280m, 1245m, 1205m, 1170m, 1150m, 1095s, 1025m, 890s, 865m cm^{-1}. *m/z* (>15%) 315 (M^+, 37%), 300 (55), 283 (20), 282 (100), 256 (34), 240 (15), 142 (18), 115 (18), 113 (16).

Analytical work

Molecular modelling studies were performed using the MSI/BIOSYM Discover package using the ESFF forcefield. All NMR spectra were collected on a Bruker DMX500 spectrometer fitted with a $^1H/^{13}C/^{15}N$ triple resonance Z-gradient probe. NOESY, DQF-COSY,[21] HSQC,[22] 2D INADEQUATE,[23] and HMBC[24] spectra were recorded using standard techniques with gradients when appropriate. The mixing time in the NOESY spectrum of **6** was 800 ms. The ^1H-^{15}N HMBC spectra were collected with a Δ delay of 100 ms. $^3J_{NH}$ coupling constants in **6** were measured from a 1D ^1H-^{15}N HSQC experiment was collected using Δ/2 delays of 50 ms and 2048 scans. Coupling constants were extracted by the method of Freeman *et al.*[25] using an eightfold *J* multiplication. ^1H and ^{13}C shifts are relative to (residual) chloroform at δ 7.25 and 77.0 respectively. ^{15}N shifts are relative to hypothetical $MeNO_2$, referenced to TMS using Ξ = 10.136783.

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