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Investigation by Two-Dimensional NMR of the Structure and Stereochemistry of a Methyl *p*-Nitrocinnamate Photodimer

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Current research in our laboratory (BG) is directed toward controlling the stereo- and regiochemistry of photochemical dimerizations. This prompted us to reinvestigate the products reported by Ishigami et al.[1] to be formed from the irradiation of (*E*)-methyl *p*-nitrocinnamate, **1**, in solution. In addition to two head-to-head dimers these authors isolated material, in low yield, which was stated to be a mixture of two head-to-tail dimers. As we had chosen to try to control the stereochemical course of this photodimerization, and as there was a continuing interest in assigning the structure and stereochemistry of photodimers, we reexamined the presumed mixture of head-to-tail dimers.

Ishigami et al. did not separate the mixture of head-to-tail dimers and appear to have based their structural assignment on the assumption that the photoproducts were derived *solely* from the methyl *E* isomer. In the absence of other evidence, the complex absorption of the cyclobutane protons at 60 Mz and the presence of two carbomethoxy resonances were consistent with their assignment. We have repeated the irradiation as described and recorded the NMR spectrum of the reported mixture at 200 and 500 MHz. At the higher fields we were able to separate the cyclobutane resonances as triplets of equal area centered at 4.81 (H-1), 4.05 (H-2), 3.99 (H-3), and 3.43 ppm (H-4). Signals from the carbomethoxy groups appear at 3.75 and 3.38 ppm and were also of equal area. Thus, the material could be a 1:1 mixture as suggested by Ishigami *or* a single compound that lacked the usual symmetry present in photodimers. This question was effectively settled by a COSY spectrum (included in supplementary material) which shows that each cyclobutane proton is coupled to two others, H-1 to H-2 and H-4 and H-3 to H-2 and H-4. This observation requires that these signals arise from a single compound. Further, the absence of cross peaks between H-1 and H-3 as well as between H-2 and H-4 shows that H-1 and H-3 are situated at opposite corners of the cyclobutane, as are H-2 and H-4.

Ishigami et al. noted,[1,2] and we have confirmed, that in addition to photodimerization, extensive *E* to *Z* isomerization occurs during the irradiation of **1**. As substantial quantities of the *Z* isomer were present in solution it appeared possible that the minor photoproducts could be derived from photoaddition reactions involving this isomer.

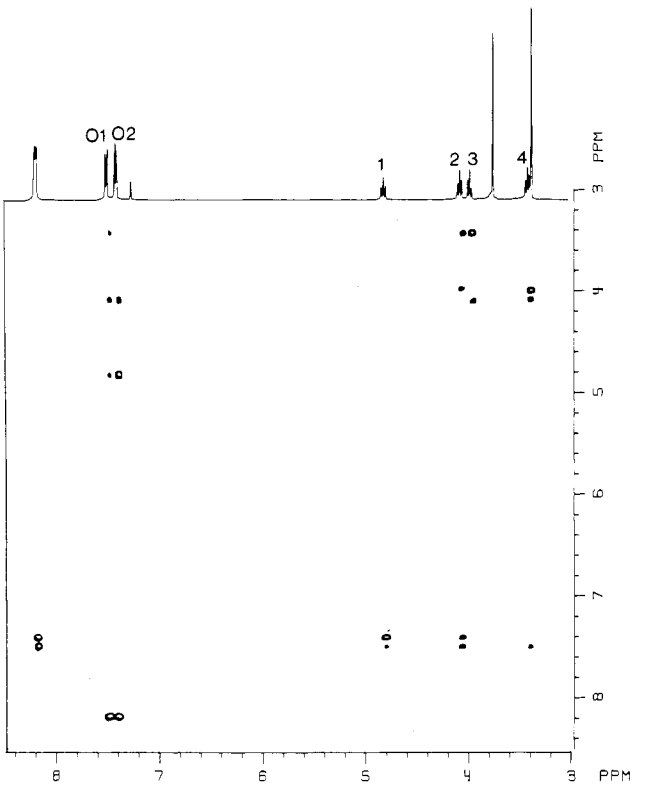
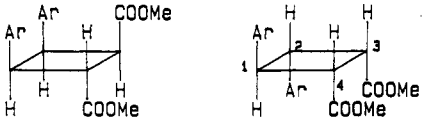


Figure 1. Absorption mode 2D NOE spectrum of **3**. The spectrum results from a 2 × 400 × 1024 data matrix, i.e., per t_1 value two sets of 1024 data points each, corresponding to odd and even numbered scans, are stored separately.[5] A mixing time of 900 ms was used, slightly shorter than the average T_1 value of the cyclobutane ring protons. Data acquisition times were 80 and 102 ms in the t_1 and t_2 dimension, respectively. Sixteen scans were recorded per t_1 value and the total measuring time was 7 h. Gaussian line broadening (5 Hz and 4 Hz) was used in the t_1 and t_2 dimensions, respectively. Only resonances with their sign opposite to the diagonal resonances are displayed. The ortho protons of the aromatic ring attached to C-1 and C-2 are labeled O1 and O2, respectively.

Inspection of the structures for the 11 possible photoadducts shows that only those for **2** and **3** lack a center, axis, or plane of symmetry which render the four cyclobutane protons and two carbomethoxy groups nonequivalent.



2 3

Ar = p-$NO_2C_6H_4$

Further structural information was obtained from a COSY experiment recorded and processed to emphasize cross peaks arising from long-range (smaller) couplings[4] (included) as supplementary material). Cross peaks were observed from couplings between H-1 and the doublet arising from aromatic ortho protons centered at 7.49 ppm in one ring and between H-2 and the doublet at 7.40 ppm, the second group of ortho aromatic protons. These results show that the aromatic rings were attached to C-1 and C-2, i.e., the photoproduct formed from head-to-head coupling

(1) Ishigami, T.; Murata, T.; Endo, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3578.

(2) Ishigami, T.; Nakazato, K.; Uehara, M.; Endo, T. *Tetrahedron. Lett.* **1979**, 863.

(3) (a) Fleming, I.; Williams, D. H. *Tetrahedron.* **1967**, *23*, 2747. (b) Paolillo, L.; Ziffer, H.; Buchardt, O. *J. Org. Chem.* **1970**, *35*, 38. (c) Jackman, L. M.; Sternhell, H. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon: New York, 1969; p 287.

(4) Bax, A. Two-Dimensional Nuclear Magnetic Resonance; Reidel: Boston, 1982; p 85.

(5) States, D. J.; Haberkorn, R. A.; Ruben, D. J. *J. Magn. Reson.* **1982**, *48*, 286.

of methyl *p*-nitrocinnamate monomers.

Information from the standard spectrum and the COSY experiments do not establish the stereochemistry of the substituents because vicinal cyclobutane protons have similar cis and trans couplings.[3] However, it is possible to assign the stereochemistry of the photoproduct from a NOESY spectrum, Figure 1, which shows interactions between H-2, H-3, and H-4. As such interactions only occur when protons are spatially close, the protons must be cis; the absence of interaction between these protons and H-1 indicates that the latter is on the other side of the cyclobutane, i.e., structure **3** is correct.

The structural and stereochemical assignment is buttressed by ancillary observations from the NOESY spectrum. The doublet at 7.49 ppm, the ortho protons of the aromatic group attached to C-1 (O_1 in Figure 1), shows polarization transfer to H-1, H-2, and H-4; the first of these is the result of a geminal interaction, while the others are vicinal (cis) interactions. Similarly, the doublet at 7.40 ppm, the ortho protons of the aromatic group attached to C-2 (O_2 in Figure 1), shows a geminal interaction with H-2 and a vicinal (cis) interaction with H-1. These observations show the aromatic rings to be trans to each other on the cyclobutane. The second COSY experiment, recorded to emphasize cross peaks arising from long-range couplings, showed a weak cross peak between the proton on C-4 and the low field *O*-methyl group. This peak indicates that the latter group is part of the carbomethoxy group attached to C-4. The higher field *O*-methyl group is therefore part of the carbomethoxy group on C-3. The upfield shift of this latter methyl group is probably caused by ring current shielding effects due to its position above the aromatic group at C-2.

The reassignment of the reported mixture as another head-to-head dimer of **1** shows that the regiochemical preference for this reaction path is greater than previously thought. There is no evidence of head-to-tail dimer formation.

Experimental Section

A solution of **1** in benzene was irradiated as described by Ishigami et al. and the mixture separated by column chromatography on silica gel. The observed chemical shifts and splitting patterns of the isolated photoproducts were in good agreement with values reported previously.[1]

Registry No. 1, 637-57-0; 3, 112420-30-1.

Supplementary Material Available: COSY spectrum of **3** (Figure 1) that shows coupling between cyclobutane protons and second COSY spectrum (Figure 2) optimized for detecting long-range couplings between ortho aromatic protons and H-1 and H-2 cyclobutane protons (4 pages). Ordering information is given on any current masthead page.

A Convenient Synthesis of 3,6-Disubstituted 3,6-Diazabicyclo[3.2.2]nonanes and 3,6-Diazabicyclo[3.2.1]octanes

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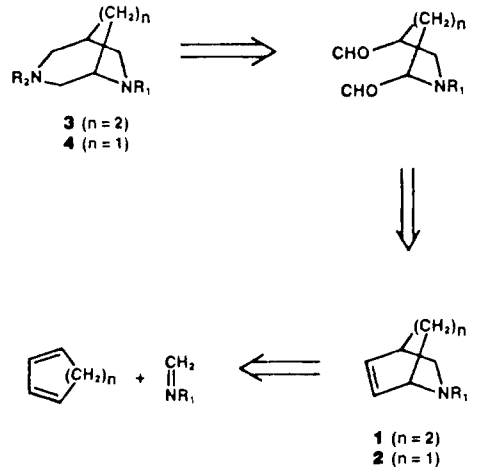
In connection with a project involving the synthesis of conformationally rigid ethylenediamine systems, we were interested in synthetic routes to 3,6-diazabicyclo[3.2.2]-nonanes (**3**) and 3,6-diazabicyclo[3.2.1]octanes (**4**). A literature search revealed that although the 3,6-diazabicyclo[3.3.1]nonane skeletal unit is present in some lupine alkaloids,[1] the simple bridged bicyclic systems **3** and **4** are unknown. We would like to describe a very convenient synthesis of these systems which allows for easy variation of the N-3 and N-6 substituents.

Retrosynthetically, 2-azabicyclo[2.2.2]oct-5-enes (**1**) and 2-azabicyclo[2.2.1]hept-5-enes (**2**) were regarded as convenient precursors to **3** and **4**, respectively, in which introduction of the 3-nitrogen of **3** and **4** could be accomplished by ozonolysis of the double bond to a dialdehyde and subsequent reductive amination.[2] The bridged, azabicyclic alkenes **1** and **2** could, in turn, be prepared by an aza Diels–Alder reaction.[3]



2-Carbethoxy-2-azabicyclo[2.2.2]oct-5-ene (**1a**), prepared by condensing 1,3-cyclohexadiene and methylene bisurethane in the presence of boron trifluoride–etherate in benzene,[4] was chosen as the aza Diels–Alder adduct precursor to the 3,6-diazabicyclo[3.2.2]nonanes (**3**). In essentially a "one-pot" procedure, a methanolic solution of **1a** was ozonolyzed at −78 °C and, after TLC analysis indicated the disappearance of starting material, the ozonide was quenched with dimethyl sulfide. The mixture was warmed to 0 °C and was treated with excess benzylamine hydrochloride and 3-Å molecular sieves and, after 4 h of stirring, excess sodium cyanoborohydride.[5] The mixture was filtered and the evaporated filtrate was carefully acidified (*HCN evolution!*) with aqueous 1 N HCl solution to destroy any amine–borane complexes and unreacted sodium cyanoborohydride. Following basification of the mixture, extractive workup, and chromatographic purification, 3-benzyl-6-carbethoxy-3,6-diazabicyclo[3.2.2]nonane (**3a**) was obtained in 33% distilled yield. Analogously, the corresponding 3-methyl analogue, **3b**, was prepared in identical yield by using methylamine hydrochloride in

(1) (a) *Chemistry of the Alkaloids*; Pelletier, S. W.; Van Norstrand Reinhold Company, New York, 1970. (b) Ohimiya, S.; Higashiyama, K.; Otomasu, H.; Haginiwa, J.; Murakoshi, I. *Chem. Pharm. Bull.* **1979**, *27*, 1055. (c) Bordner, J.; Ohmiya, S.; Otomasu, H.; Haginiwa, J.; Marakoshi, I. *Chem. Pharm. Bull.* **1980**, *28*, 1965.

(2) During the course of our synthetic investigations, a similar ozonolysis–reductive amination strategy was reported for the synthesis of 7,8-dicarbomethoxy-8-oxa-3-azabicyclo[3.2.1]octane, see: Kawaguchi, M.; Ohashi, J.; Kawakami, Y.; Yamamoto, Y.; Oda, J. *Synthesis* **1985**, 701. More recently, these authors have prepared piperazines and thiomorpholines by the same method, see: Kawaguchi, K.; Hayashi, O.; Hamada, M.; Yamamoto, Y.; Oda, J. *Agric. Biol. Chem.* **1987**, *51*, 435.

(3) For an excellent review, see: Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949.

(4) (a) Cava, M. P.; Wilkins, C. K.; Dalton, D. R.; Bessho, K. *J. Org. Chem.* **1965**, *30*, 3772. (b) Borne, R. F.; Clark, R.; Holbrook, J. *J. Med. Chem.* **1973**, *16*, 853.

(5) Excess amine hydrochloride (10 equiv) and sodium cyanoborohydride (2.5 equiv) were used routinely, and no attempt was made to perform the reaction with more stoichiometric amounts of reagents.

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