with 0.70 g (3.2 mmol) of **3Z**, 14.9 mL of concentrated HCl, 11.4 mL of H_2O, and 11.4 mL of HOAc (glacial). After distillation of 12 mL from the reaction mixture and extraction of the remainder with ether, 0.51 g of crude **1Z** was obtained. Crystallization from EtOH/ether gave 0.42 g (78%) of pure **1Z**·HCl: mp 187 °C dec; NMR (CD_3OD) δ 4.0 (m, 1 H, C(2)-H), 2.2 and 1.8 (m, 2 H, C(3)-H).

Anal. Calcd for $C_4H_7Cl_2NO_2$: C, 27.93; H, 4.10; N, 8.14; Cl, 41.22. Found: C, 28.10; H, 4.41; N, 8.12; Cl, 41.07.

Acknowledgment. We are grateful for the generous support of NIDA Grant No. DA 02938 and NSF Grant No. CHE 8122011.

Registry No. **1E**·HCl, 89363-83-7; **1Z**·HCl, 89363-84-8; **2E**, 89363-85-9; **2Z**, 89363-86-0; **3E**, 89363-87-1; **3Z**, 89363-88-2; **4**, 89363-89-3; 2-phenyl-4-(ethoxymethylene)-5(4*H*)-oxazolone, 15646-46-5; 2-phenyl-4-(hydroxymethylene)-5(4*H*)-oxazolone, 65037-88-9; hippuric acid, 495-69-2; ethyl orthoformate, 122-51-0.

Nitration of Methyl 2-Furoate with Acetyl Nitrate. On the Configurations of Six Isolated Intermediary Adducts

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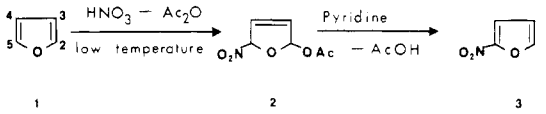
Reaction of methyl 2-furoate with acetyl nitrate afforded the isolation of six adducts whose stereochemistry was determined: (*E*)- and (*Z*)-2-carbomethoxy-2-acetoxy-5-nitro-2,5-dihydrofuran, (*E*)- and (*Z*)-2-carbomethoxy-4-acetoxy-5-nitro-4,5-dihydrofuran, and the new compounds (*E*)- and (*Z*)-2-carbomethoxy-4-nitroxy-5-nitro-4,5-dihydrofuran. The value of ^1H NMR technique in the structure determination of these compounds was demonstrated.

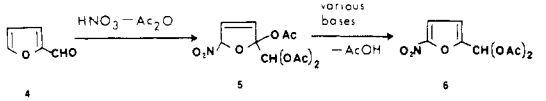
Since the beginning of this century it has been known that attempts to nitrate furan (**1**) with fuming nitric acid



1 2 3

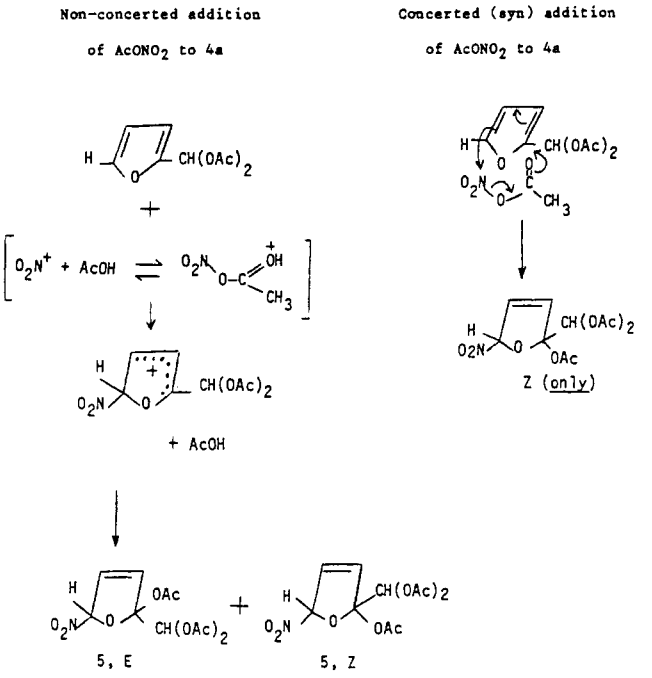
in acetic anhydride lead to the formation of a rather stable intermediate, subsequently characterized as 2-acetoxy-5-nitro-2,5-dihydrofuran (**2**) which can be converted into 2-nitrofuran (**3**) by the action of mild base.[2,3] The isolation of this intermediate drew immediate attention since it represented at that time a contrast to the direct nitration of benzene. The structure and mode of decomposition of the intermediate were studied in considerable detail[4,5] in order to elucidate the mechanism of nitration of furan. Various structures were proposed but it was not until 1947 that structure **2**, proposed by Freure and Johnson[4] in 1931, was established.[5]

Analogous nitro acetates have since been isolated as intermediates in the nitration of several furan derivatives.[4,6-8] Under similar conditions furfural (**4**) was converted into the crystalline nitration intermediate **5**.



4 5 6

Scheme I



Crystalline **5** was assumed to be a single isomer. The stereochemical relationship between the 5 and 2 asymmetric centers was not studied until 1978 when Greene and Lewis[9] reported the characterization of **5** as a single compound by means of ^1H NMR. They suggested it to be the product of syn addition of acetyl nitrate, in line with the report of Bordwell and Garbisch that treatment of alkenes in general[10a] and, specifically, cyclopentadiene, 1-phenylcyclopentene, and 1-phenylcyclohexene,[10b] with acetyl nitrate yields the product of syn addition. However,

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(2) Acheson, R. M. "An Introduction to the Chemistry of Heterocyclic Compounds", 2nd ed.; Interscience: New York, 1967; p 100.
(3) Marino, G. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1971; Vol. 13, pp 254–255.
(4) Freure, B. T.; Johnson, J. R. *J. Am. Chem. Soc.* **1931**, *53*, 1142–1147.
(5) Clauson-Kaas, N.; Fakstorp, J. *Acta Chem. Scand.* **1947**, *1*, 210–215.
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(7) Lola, D. O.; Venters, K. K.; Hillers, S. A. *Latv. PSR Zinat. Akad. Vestis, Kim. Ser. Riga.* **1976**, *4*, 431–435; *Chem. Abstr.* **1977**, *86*, 55217g.
(8) Lola, D. O.; Venters, K. K.; Liepins, E. E.; Hillers, S. A. *Khim. Geterotsikl. Soedin.* **1975**, *7*, 883–889; *Chem. Abstr.* **1976**, *84*, 4749h.
(9) Greene, B. B.; Lewis, K. G. *Aust. J. Chem.* **1978**, *31*, 627–638.
(10) (a) Bordwell, F. B.; Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 3588–3598. (b) Garbisch, E. W., Jr., unpublished results noted in ref 10a.

0022-3263/84/1949-1636$01.50/0

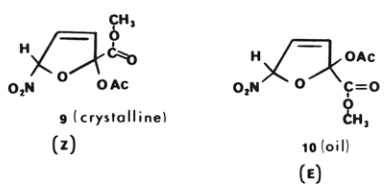
Bordwell and Garbisch later *corrected* the stereochemical assignments for the nitro acetates obtained from the reaction of 1-phenylcyclopentene and 1-phenylcyclohexene[11] when they found that the major nitro acetate formed in either case was actually that from anti addition. These authors then concluded that, generally, anti additions are as common as syn additions in these reactions with acetyl nitrate. Thus, the stereochemistry of compound **5** as well as that of related compounds assigned a priori by the method of Greene and Lewis[9] may not be correct.

However, Bordwell and Garbisch did *not* change their report that cyclopentadiene gives *exclusively* the product of the syn addition. If the original results are valid, then, there may be something special about cyclopentadiene compared to other cyclic and acyclic alkenes which generally afford mixtures of syn and anti adducts. It may be asked then, if there is something special about the furan system which may also give only the product of syn addition. The literature reports of the nitration of various furans point to this conclusion since generally the isolation of *one* adduct is reported. If indeed only the syn nitro acetate adduct is obtained it would strongly support the concerted syn addition mechanism as the sole pathway (Scheme I). Isolation of syn *and* anti adducts, however, would suggest a nonconcerted nitronium ion initiated addition mechanism (Scheme I), perhaps in conjunction with the concerted syn addition.

It was important, therefore, to learn whether more than one nitration intermediate is formed during the nitration treatment of furans with acetyl nitrate. A good candidate for this study was methyl furoate (**7**), since, in their 1931 report on the nitration of **7**, Freure and Johnson[4] made some observations indicating the possibility that two or even more isomeric adducts were formed.

Freure and Johnson observed that reaction of acetyl nitrate with methyl furoate (**7**) provided a white crystalline product along with a heavy yellow oil. The crystals, identified by elemental carbon–hydrogen analysis as an "intermediate nitroacetate", were found to decompose almost quantitatively into methyl 5-nitrofuroate (**8**), when treated with pyridine at elevated temperatures. The oil, however, underwent a violent exothermic reaction when warmed briefly with pyridine, to provide **8** also, but in only 25–30% yield.

In 1971 the reaction of **7** with acetyl nitrate was reinvestigated by one of us and it was proposed that the crystalline product and the oil represent different geometric isomers, the crystals having the *Z* configuration (**9**)



and the oil the *E* configuration (**10**).[12] This proposal was based on the observation again that the oil underwent pyridine-induced elimination more readily than the crystals and that the oil, therefore, afforded the more favored syn elimination with this base.

More recently Hillers et al.[8] also studied the reaction of **7** with HNO_3–Ac_2O, but with H_2SO_4 as catalyst. While they obtained both oil and crystalline products, the latter predominated (>53%). On the basis of NMR studies they

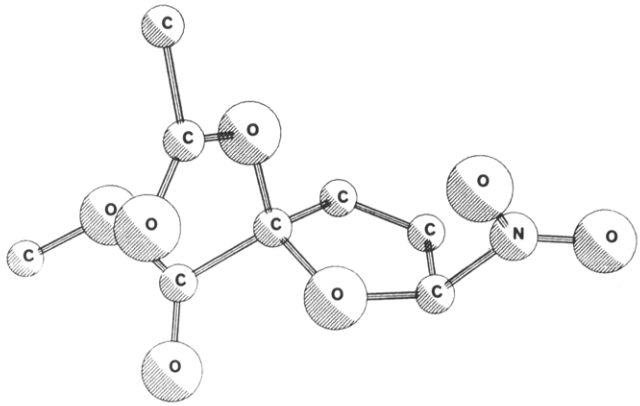
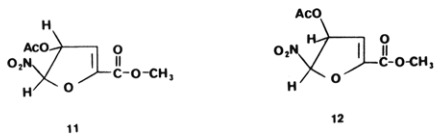


Figure 1. A stereoview of a single crystal of **9** as revealed by X-ray crystallography (this study).

suggested a *Z* configuration (**9**) for the crystals, and reported that the oil was a mixture of **9** and **10** in addition to the "1,2-adducts" **11** and **12**. No yields were noted for



any of these products. Their ^1H NMR evidence for isomer identification was not conclusive, however, and in a later paper Hillers et al.[7] described the crystalline adduct without assigning a definite geometry.[13]

In order to elucidate the mechanism of this reaction we decided to (a) determine the structure of the crystals (**9**) *unequivocally*, and (b) characterize **10**–**12** and to measure their yields to establish which one, if any, is formed to a similar extent as **9**.

We have determined the structure of the crystals (**9**) by X-ray crystallography. Compound **9** is indeed the syn (*Z*) adduct proposed by Kolb[12] in 1971 and suggested by Hillers et al.[8] in 1975. A stereoview of a crystal of **9** is shown in Figure 1.

Very recently we became aware of a report by Venters et al.[14] (Hillers co-workers) on the X-ray structure determination of **9**. Their results, essentially the same as ours, support the syn (*Z*) structure. In the same report Venters et al. referred to their X-ray structural identification[15] of intermediate **5** in the nitration of furfural (**4**). In contrast to **9**, **5** is the anti (*E*) adduct. The latter stereochemistry is reasonable since there is considerably more bulk at C-2 in furfural diacetate (**4a**) which is the precursor of **5** than in **7** which disfavors the concerted syn addition in the case of **4a**. Also, a true carbocationic intermediate leading to anti addition, is electronically favored in **4a** but disfavored in **7** (Scheme I).

Since X-ray structure determinations are expensive, elaborate, time consuming, and require the crystalline forms, we decided to explore the value of various ^1H NMR techniques in determining the structure of all the intermediates formed in the reaction of furans with acetyl nitrate.

(11) Bordwell, F. B.; Garbisch, E. W., Jr. *J. Org. Chem.* **1963**, *28*, 1765–1769.

(12) Kolb, V. M. B. S. Thesis, Belgrade University, 1971 (research directed by Prof. B. Bastić).

(13) Prof. Solomon Hillers died in 1975. It is possible, therefore, that some aspects of this group's work in this area may have been incomplete at that time.

(14) Venters, K. K.; Kemme, A. A.; Bleidelis, J. J. *Latv. PSR Zinat. Akad. Vestis, Kim. Ser* **1980**, *4*, 479–83; *Chem. Abstr.* **1981**, *94*, 14940j.

(15) Venters, K. K.; Mishnev, A. F.; Bleidelis, J. J. Third International Symposium on Furan Chemistry, Smolenice, Czechoslovakia, 1979; Abstract p 49. We could not find this work or even a listing of it in the above book of abstracts, however. The X-ray structure of **5** anti adduct was published later: Mishnev, A. F.; Bleidelis, J. J.; Venters, K. K. *Tetrahedron* **1980**, *36*, 1817–1820.

Table I. Products from the Reaction of Methyl 2-Furoate (7) with Acetyl Nitrate[a]

product	yield, %[c]	^{1}H NMR[b] chemical shifts, δ C(O)OCH$_3$	OC(O)CH$_3$	3-H	4-H	5-H	coupling constants, Hz J_{34}	J_{45}	J_{35}
9	26	3.83	2.18	6.45	6.53	6.41	5.77	1.60	−1.61
		(3.78	2.13	6.59	6.76	6.65	5.77	1.61	−1.58)
10	20	3.84	2.12	6.64	6.50	6.49	5.91	1.49	−1.75
		(3.79	2.11	6.70	6.69	6.75	5.31	2.18	−1.71)
12	7	3.86	2.14	7.08	6.45	6.59	1.22	5.80	−0.92
		(3.89	2.11	7.10	6.70	6.74	1.22	5.83	−0.92)
11	7	3.92	2.14	7.31	6.48	6.54	1.13	5.83	−1.41
		(3.91	2.11	7.31	6.73	6.71	1.0	6.0	−1.4
14	2	3.91		7.19	6.39	6.72	1.33	5.78	−1.18
13	2	3.92		7.41	6.42	6.66	1.24	5.80	−1.54
8	12	3.98		7.30	7.35		3.85		

[a] Preformed acetyl nitrate (HNO_3 + Ac_2O, −10 to −5 °C); reaction carried out at −10 to −5 °C. The IR and MS data of all the products are in agreement with the proposed structures. [b] In $CDCl_3$; data in parentheses in acetone-d_6. [c] Yield of 9 represents isolated products; yields of other products were approximated from the NMR spectrum of residual oil after removal of 9 but before chromatographic fractionation because 10–14 partially decomposed into 8 during chromatography (see Experimental Section).

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover capillary melting point apparatus. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. NMR spectra were taken on Perkin-Elmer R32 (90 MHz) and Nicolet NT-200 FT-NMR (200 MHz) spectrometers; IR spectra were recorded on Beckman IR-10 and Perkin-Elmer 297 spectrophotometers; and mass spectra were taken on DuPont 21-491 BR and Finnegan MS 3300 spectrometers.

Reaction of Methyl 2-Furoate (7) with Acetyl Nitrate. The general method of Marquis[16] and Freure and Johnson[4] was followed. Methyl 2-furoate (7) was prepared by esterification of 2-furoic acid (MCB Practical Grade, mp 130–134 °C) with anhydrous methanol and purified by fractional distillation, bp 180–182 °C; IR and ^{1}H NMR spectra were identical with those shown for this compound in the Aldrich Library of Spectra. Acetyl nitrate was prepared by the dropwise addition of fuming nitric acid (B & A, d = 1.59–1.60, 17.5 g, 0.25 mol) to cold (−10 to −5 °C) acetic anhydride (MCB, ACS Reagent Grade, 27.0 g, 0.27 mol), the mixture being maintained at −10 to −5 °C during the addition (ca. 4 h) and until ready for use. A cold (−5 °C) solution of 7 (5.50 g, 0.044 mol) in acetic anhydride (10.3 g, 0.10 mol) was added dropwise over a 45-min period to the cold acetyl nitrate, the mixture being stirred and rigorously maintained at −10 to −5 °C during the addition and at ca. −5 °C for 1 h thereafter. The mixture was poured into crushed ice from which a mass of white crystals and yellow oil separated. This entire mixture was extracted with ether and the combined extracts were washed with water until the washings were no longer acidic, dried ($MgSO_4$), and evaporated leaving 7.1 g of a mixture (oil and crystals) shown by NMR to be composed of 8–12; the presence of the very small amounts of 13 and 14 was not apparent until they were separated.

Separation and Identification of Products. The mixture of oil and crystals was triturated with ice-cold ether, leaving a mass of white crystals; it was shown by NMR that essentially all of the crystalline product was separated from the oil this way. The crystals, 2.6 g (26% yield), mp 82–88 °C, were recrystallized from anhydrous methanol to constant mp 100–101 °C (lit.[8] 100–101 °C and lit.[4] 96 °C), and unambiguously identified as (*Z*)-2-carbomethoxy-2-acetoxy-5-nitro-2,5-dihydrofuran (9) by X-ray analysis (this study, Figure 1; cf. ref 14). NMR spectral data are given in Table I.

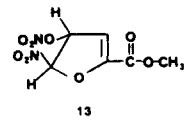
The ether solution from the trituration was evaporated leaving a yellow oil, 4.3 g. The absence of 9 as determined by ^{1}H NMR greatly facilitated quantitative interpretation of the NMR spectrum of the oil, which was thus shown to be composed of about 44 mol% of (*E*)-2-carbomethoxy-2-acetoxy-5-nitro-2,5-dihydrofuran (10, 2.0 g, 20% yield), about 15 mol% each of (*E*)- and (*Z*)-2-carbomethoxy-4-acetoxy-5-nitro-4,5-dihydrofuran (11 and 12, 1.4 g, 7% yield, of each isomer), and 26 mol% of methyl 5-nitro-2-furoate (8, 0.9 g, 12% yield). With similar mixtures from other runs it was found that 10, 11, and 12 readily decomposed into 8 when subjected to fractional distillation (0.02 mm, ca. 100–137 °C), TLC on silica gel,[8] or column chromatography on silica gel (Fisher, 60–200 mesh, grade 950). From the latter, while 80% decomposition resulted, some 10 was isolated free from 8 but contaminated with small amounts (<10%) of 11 and 12 whose presence precluded a worthwhile high-resolution analysis of the ^{1}H NMR spectrum exhibited by 10 so isolated.

Ultimately, flash chromatography[17] provided more reasonable results. In this way, from a column packed with silica gel (E. Merck 60, 230–400 mesh) and eluted with a 1:1 solution of benzene–methylene chloride, 40 fractions (25 mL each) were collected and monitored by ^{1}H NMR. From the initial fractions the two isomeric 2-carbomethoxy-4-nitroxy-5-nitro-4,5-dihydrofurans were isolated, the less polar (faster eluting) isomer, 13, being assigned the trans (*E*) configuration and the more polar, 14, the cis (*Z*) configuration (see Discussion). Since these products were not detected in the NMR spectrum of the oil, they constituted less than 5 mol%, tantamount to a yield of no more than 2% each. Pure 8 was then eluted as a fraction although it was also continuously eluted in other fractions thereafter, being formed on the column via silica-catalyzed elimination reactions of 10–12 (and probably of 13 and 14). When recrystallized from methanol 8 exhibited mp 80–81.5 °C (lit.[4] mp 81.6 °C). The two isomeric 5-nitro-4-acetates were next eluted, the less polar 11 (trans) being followed by 12 (cis). Finally, 10 was eluted. Although 10, 11, and 12 were thus separated from each other, each contained at least 30 mol% of 8; this contamination, however, did not interfere with the respective high-resolution ^{1}H NMR analysis of these compounds. The NMR spectral data exhibited by these products are compared in Table I.

The IR and MS data of all the products are in agreement with the proposed structures. The C,H,N elemental analysis for 9 was satisfactory.

Results and Discussion

The reaction was carried out as described in the Experimental Section. Products were separated and identified as noted below. The structures of the two new compounds, 13 and 14 are illustrated.



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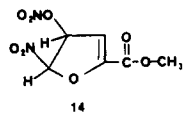

14

^{1}H NMR Analysis. The chemical shifts and coupling constants listed in Table I represent the best values ob-

(16) Marquis, R. *Ann. Chim. Phys.* **1905**, *4*, 216–238.

(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

tained from an iterative fit of the observed to calculated lines. A modified version (ITRCAL) of the LAOCOON III program[18] written for the Nicolet 1180 computer was used for the calculation. In all cases the match between observed and calculated spectra was excellent.

The ring protons of all the adducts gave rise to ABC spectra. In the cases of the 2,5-adducts (**9** and **10**) the protons are tightly coupled and the calculated spectra are sensitive to the relative signs of the coupling constants. The best fit to the observed spectrum is obtained with one of the small couplings assigned a negative value, and this is most reasonably associated with the transannular four-bond (J_{35}) interaction. This information and the fact that coupling between two vinylic protons (J_{34}) is the largest allows the unique assignments of all the δ and J values. The assignments in the case of **9** were verified by a set of spin-tickling experiments. The lines in the spectrum of **10** were not well enough resolved to permit successful spin tickling in that case.

The four 4,5-adducts (**11–14**) have only one vinylic proton, 3-H, and it is reasonably assigned the lowest field resonance in each case. Of the remaining two ring protons the lower field one was tentatively assigned to 5-H whose carbon atom is bonded to NO_2 and the ring oxygen. Unfortunately, the relative signs of the coupling constants in these cases could not be obtained by a comparison of observed and calculated spectra. It was necessary, therefore, to use the spin-tickling technique and it was applied to one isomer of each pair, specifically **12** and **14** (insufficient amounts of **11** and **13** precluded their study by this technique). Again, one of the small couplings is negative and can reasonably be assigned to the J_{35} transannular coupling. Thus, for **12** and **14** the respective resonances of 5-H and 4-H as well as J_{45} and J_{34} were unambiguously assigned and the tentative assignments to 5-H and 4-H in these isomers were confirmed. By analogy, the respective assignments to **11** and **13** were made.

The data in Table I show that it is now easy to identify any one of the isolated products as a 2-acetoxy-5-nitro adduct (**9**, **10**), a 4-acetoxy-5-nitro adduct (**11**, **12**), a 4-nitroxy-5-nitro adduct (**13**, **14**), or the nitrated substrate (**8**), simply from the chemical shifts in $CDCl_3$. Thus, in **9** and **10** the three ring protons have very similar values, all falling within a range of 0.15 ppm, while in **11** and **12** 3-H is shifted substantially downfield from the other two ring protons (by at least 0.5 ppm). The latter effect is also exhibited by **13** and **14**; these adducts are further distinguishable by the absence of OAc resonance from their spectra. The pattern exhibited by **8** is self-identifying.

The NMR data in Table I for the diastereomers **9** and **10** give no obvious clues to the respective geometries. It might be pointed out that for **9** in $CDCl_3$ or acetone-d_6 vinylic proton 4-H is less shielded than vinylic proton 3-H; for **10** the reverse order is exhibited in $CDCl_3$ while the two protons are equally shielded in acetone-d_6. Although these differences reflect the stereochemical differences between these two isomers, they must be strongly associated with the particular substituents. It would be presumptuous, therefore, to generalize cis–trans assignments of related isomers on the basis of this difference exhibited in this one case.

On the other hand, for the isomer pairs **11**, **12** and **13**, **14** one would expect that coupling of the protons on the vicinal sp^3 carbons (J_{45}) would be substantially larger for the cis isomers (dihedral angle of ca. 0°) than the respective trans isomers (dihedral angle of ca. 90°) as is often the case with cyclopentanes and defined by the Karplus equations for the simpler cases.[19] The fact that **11–14** *all* exhibit essentially the identical value for J_{45} precludes the use of this method for cis–trans differentiation in these cases. In comparing the ^1H NMR spectra of **11** and **12** in pyridine-d_5 Hillers drew the same conclusion.[8] With both pairs of these isomers in $CDCl_3$ or acetone-d_6, however, 3-H is less shielded in the trans isomer than in the cis isomer by about 0.23 ppm (cf. **11** with **12** and **13** with **14**). Hillers' data for **11** and **12** in either acetone-d_6 or pyridine-d_5 likewise show this substantial difference in 3-H shielding between these isomers, although he did not associate it with cis–trans assignments.[8] Since this effect is now shown to be exhibited by both pairs of these similar isomers and is apparently indifferent to specific solvent interactions, it might prove to be generally useful in differentiating between cis and trans isomers of this type.

(18) Castellano, S.; Bothner-By, A. A. *J. Chem. Phys.* **1963**, *41*, 3863–3869.

(19) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11–15; *J. Am. Chem. Soc.* **1963**, *85*, 2870–2871.

(20) **Note Added in Proof**: According to an ^{15}N NMR study, **5** is formed as a 7:1 mixture of anti:syn adducts: Liepins, E. E.; Zolotoyabko, R. M.; Stradins, J. P.; Trushule, M. A.; Venters, K. K. *Khim. Geterotsikl. Soedin.* **1980**, *6*, 741–743; *Chem. Abstr.* **1980**, *93*, 220008u.