17.7 g (0.14 mol) of Na_2SO_3 in 60 ml of H_2O: yield 30.6 g (91.0%). Crude $Br(CH_2)_4SO_3Na$ (30.0 g, 0.13 mol) and 600 ml of concentrated NH_4OH were allowed to react in the same way as **2**: yield 13.3 g (69.0%); mp 251–252° dec.

ε-Aminopentanesulfonic Acid (5). $Br(CH_2)_5Br$ (100.0 g, 0.435 mol) in 200 ml of 95% EtOH and 60 ml of H_2O was treated with 16.8 g (0.133 mol) of Na_2SO_3 in 60 ml of H_2O: yield 29.9 g (89.0%). Crude $Br(CH_2)_5SO_3Na$ (22.0 g, 0.087 mol) was treated with 700 ml of concentrated NH_4OH in the same way as **2**: yield 10.8 g (74.0%); mp 311–312°.

β-Guanidinoethanesulfonic Acid (6). Into a solution of 6.3 g (0.05 mol) of **2** in 30 ml of concentrated NH_4OH, 10.1 g (0.05 mol) of *S*-ethylisothiourea · H_2SO_4 was added. The mixture was heated to 65° and stirred vigorously until the reactants dissolved. There was a vigorous evolution of C_2H_5SH and the mixture was allowed to cool to room temperature. The reaction mixture was concentrated to dryness in vacuo. The residue was dissolved in H_2O and insoluble unreacted *S*-ethylisothiourea was filtered off. The filtrate was then concentrated in vacuo to dryness. Ion-exchange chromatography with a 2.2 × 40 cm column of AG 1 X8 resin, 100–200 mesh, OH^- form, was used for the purification of **6**. NH_4OH (2 *N*), 0.5 *N* NH_4OH, and then H_2O were used successively as effluent solutions. Compound **2** was found in fractions 4–7. Fractions containing **6**, 10–70, were pooled and concentrated in vacuo. The dry residue was treated with H_2O–EtOH and kept at 5° to obtain fine, white crystals: yield 4.0 g (48.0%); mp 266–267°.

γ-Guanidinopropanesulfonic Acid (7). A mixture of 5.2 g (0.04 mol) of **3**, 8.1 g (0.04 mol) of *S*-ethylisothiourea · H_2SO_4, and 25 ml of concentrated NH_4OH was treated in the same manner as **6**: yield 4.2 g (57.9%); mp 239–240°.

δ-Guanidinobutanesulfonic Acid (8). A mixture of 1.53 g (0.01 mol) of **4**, 2.20 g (0.01 mol) of *S*-ethylisothiourea · H_2SO_4, and 10 ml of concentrated NH_4OH was treated in the same way as **6**: yield 0.84 g (43.0%); mp 222–223°.

ε-Guanidinopentanesulfonic Acid (9). A mixture of 5.0 g (0.03 mol) of **5**, 6.1 g (0.03 mol) of *S*-ethylisothiourea · H_2SO_4, and 25 ml of concentrated NH_4OH was allowed to react in the same manner as **6**: yield 2.1 g (33.5%); mp 257–258°.

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Carbon-13 Magnetic Resonance Spectroscopy of Drugs. Sulfonamides

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The natural abundance ^{13}C magnetic resonance spectra of a series of sulfonamide drugs (sulfanilamide, sulfaguanidine, sulfathiazole, sulfasuxidine, sulfadiazine, sulfamerazine, sulfamethiazine, and sulfapyridine) have been determined at 25.15 MHz employing the pulse Fourier transform technique. The chemical shifts have been assigned with the aid of off-resonance and selective proton decoupling techniques, as well as by long-range carbon-13 proton coupling patterns.

Proton magnetic resonance (^1H NMR) spectroscopy has been used widely for structural studies of medicinally important molecules and for substrate–macromolecule binding studies.[1] Nevertheless, ^1H NMR spectra are often too complex to be helpful in the detailed structure analysis. This complexity results from the limited spectral range and from extensive spin–spin coupling. Therefore, the usefulness of ^1H NMR in structural studies of complicated mole-

Table I. ^{13}C NMR Chemical Shifts[a] in DMSO Solution

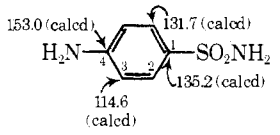
Carbon	I	II	III	IV	V	VI	VII	VIII
1	131.3	131.0	128.0	136.4	125.0	125.3	125.3	126.0
2	128.4	127.9	128.0	127.4	130.3	130.4	130.5	129.1
3	113.6	113.0	112.8	118.9	112.4	112.4	112.1	112.8
4	152.5	151.9	152.4	142.8	153.2	153.2	153.0	152.8
1′		158.3	168.2	169.1	158.4	157.2	156.8	152.5
3′			124.4	124.7	159.4	165.2	167.4	146.3
4′			107.7	108.4	115.6	114.9	113.8	117.2
5′					159.4	157.8	167.4	139.0
6′								112.4
CH_3						23.0	23.2	

[a] Parts per million downfield from Me_4Si.

cules and molecular complexes has some serious limitations. Carbon-13 magnetic resonance (^{13}C NMR) spectroscopy, on the other hand, has recently been shown to be a powerful physical technique for determining the structure, configuration, and conformation of organic compounds.[2] In particular, ^{13}C NMR applications in biosynthetic studies[3] and in the structure elucidation of natural products[4] and drugs[5] have received attention. In conjunction with specific labeling by isotope enrichment, ^{13}C NMR spectroscopy will undoubtedly become one of the more prominent methods in future studies of drug–receptor interactions. The present paper reports an investigation of the application of pulse Fourier transform ^{13}C NMR to the structural analysis of sulfonamide drugs, one of the most important groups of antimicrobial agents.

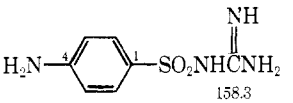
The spectral data of eight sulfa drugs recorded in dimethyl sulfoxide solution are summarized in Table I. The ^{13}C resonances were generally assigned by combinations of the following methods: (1) chemical shift values expected for specific types of carbons[2] from the broad-band proton noise decoupled spectrum, which also accounts for the approximate number of carbon nuclei from the relative peak intensity and shape; (2) determination of the number of protons directly attached to each carbon atom from the single-frequency off-resonance proton decoupled spectrum; (3) selective proton decoupling experiments for carbons attached to protons with independently assigned ^1H NMR spectral data.

The aryl carbon shieldings are sensitive to the electronic and steric effects of substituents. From the results for a large variety of substituted benzenes, the shielding values or substituent effects have become available.[2,6] It is well recognized that the effects of individual substituents of aromatic molecules appear to be additive for polysubstituted compounds. Based on the shielding values of amino and sulfonamide groups, the chemical shifts of sulfanilamide (I) can be calculated.



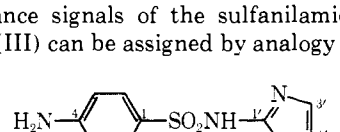
I

The calculated values permit us to assign the observed signals at 152.5 and 113.6 ppm to C_3 and C_4. The C_1 and C_2 resonances can be distinguished from their relative intensity and the multiplicity of the off-resonance proton decoupled spectrum. Additionally, these assignments were confirmed by selective single-frequency proton decoupling experiments [irradiate at δ_H = 6.64 (C_3-H) and 7.50 (C_2-H) ppm, respectively]. Sulfanilamide can then be utilized as a model compound for chemical shift assignments of C_1, C_2, C_3, and C_4 of sulfaguanidine (II). The only remaining peak at 158.3 ppm is the guanido carbon signal.

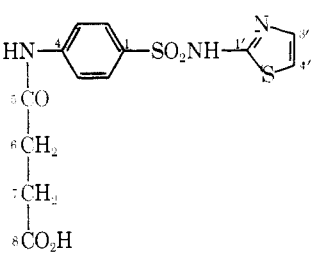


II

The resonance signals of the sulfanilamide portion of sulfathiazole (III) can be assigned by analogy to sulfaguanidine (II) and sulfanilamide (I). The C_1 signal accidently overlaps with the signal for C_2 (Figure 1, A) but they can be differentiated in the off-resonance proton decoupled spectrum (Figure 1, B). The C_2 signal is split into a doublet while the C_1 signal remains unchanged. The most downfield singlet at 168.2 ppm is assigned to the $C_{1'}$ resonance. The two doublets of 124.4 and 107.7 ppm can be assigned to $C_{3'}$ and $C_{4'}$, respectively, on the basis of the electronegativity of the adjacent heteroatoms. The selective proton decoupled spectra further substantiate this conclusion [irradiate at δ_H = 6.63 (C_3-H and $C_{4'}$-H), 7.15 ($C_{3'}$-H), and 7.68 (C_2-H) ppm, respectively] (Figure 1, B–D). These firm assignments make the spectral interpretation of the thiazole moiety of sulfasuxidine (IV) straightforward. From the



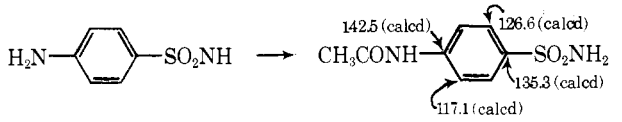
III



IV

shielding values of amino and acetamide substituents of benzene,[2,6] and the assigned chemical shifts of sulfanilamide, the expected chemical shift values can be calculated for N_4-acetylsulfanilamide, which serves as an appropriate model for the C_1, C_2, C_3, and C_4 assignments. The remaining four peaks at 174.3, 171.2, 31.6, and 29.1 ppm may be

assigned to the C_5, C_8, C_6, and C_7 signals on the basis of simple chemical shift theory.[2]

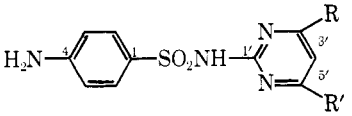


Single-frequency off-resonance proton decoupling has become a routine procedure for the assignment of ^{13}C resonance signals.[7] The resulting ^{13}C spectrum retains nuclear Overhauser enhancements found in broad-band proton noise decoupled spectra but indicates splitting mainly resulting from the large one-bond ^{13}C–H coupling constants. These splittings, called reduced coupling constants ($J_{red.}$), are smaller than the actual coupling constants (J)

$$J_{red.} = \Delta f_H \cdot J/\not{\propto}H_2$$

where $\not{\propto}H_2$ is the intensity of the decoupling field, $\Delta f_H = f_H^{irradiation} - f_H^{resonance}$. Very little attention has been paid to the long-range coupling. Figure 1 (E) shows the downfield region of the single-frequency off-resonance decoupled spectrum of sulfathiazole (irradiate at δ_H = 10 ppm). In addition to the normal large one-bond splittings, it is observed that the singlets at 168.2 ($C_{1'}$), 152.4 (C_4), and 128.0 (C_1) ppm have become a double doublet, a triplet, and a triplet, respectively. These small splittings arise from the three-bond coupling. In aromatic compounds, the two-bond coupling constant $^2J_{CCH}$ is usually smaller than the three-bond coupling constant $^3J_{CCCH}$.[8] The reduced splitting, $^2J_{CCH}$, is too small to be detected in the normal single-frequency decoupling experiment. These distinct splittings provide valuable information, particularly for quaternary carbons. Thus, $C_{1'}$ can be easily distinguished from C_1 and C_4 by its specific splitting, a doublet of doublets instead of a triplet, due to the nonequivalence of the protons attached to $C_{3'}$ and $C_{4'}$, $\Delta f_{4'\text{-}H} \neq \Delta f_{3'\text{-}H}$, which results in different reduced long-range coupling constants. The further application of this unique splitting is illustrated in the spectral interpretation of sulfapyridine (VIII).

In pyrimidyl sulfonamide drugs, all the carbon resonances of the sulfanilamide portion can be directly assigned by comparison with the chemical shift patterns of the above sulfonamide compounds. Of the carbon atoms of the pyrimidine unit of sulfadiazine (V), $C_{1'}$ can be expected



V, R = H; R′ = H
VI, R = CH_3; R′ = H
VII, R = CH_3; R′ = CH_3

to resonate at rather low field and is assigned the singlet at 158.4 ppm. The remaining two doublets at 159.4 and 115.6 ppm can be assigned on the basis of their proximity to the nitrogen atoms and their relative intensity (2:1). These assignments are in good agreement with the previous study of the model compound, pyrimidine.[9] The known α-, β-, and γ-effects of the methyl group[9] allow us to assign the lowest field signals of sulfamerazine (VI) and sulfamethiazine (VII) to $C_{3'}$. This leaves the most upfield remaining aromatic peak to be designated $C_{4'}$. The resonance at 157.8 ppm is therefore the $C_{5'}$ signal of sulfamerazine.

For sulfapyridine (VIII), the sulfanilamide resonances were assigned following the arguments presented above.

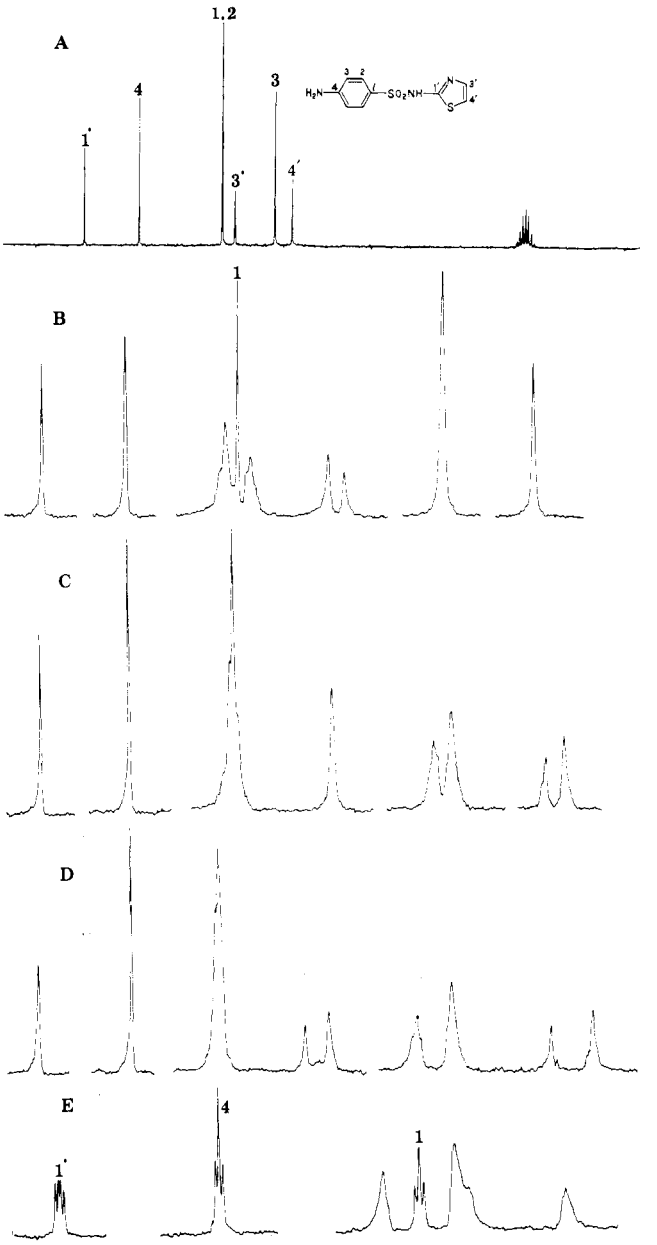
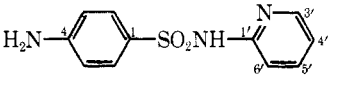
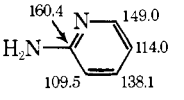


Figure 1. ^{13}C NMR spectrum of sulfathiazole in DMSO-d_6: A, broad-band proton decoupled; B–D, selectively proton decoupled by irradiation at δ_H = 6.68, 7.15, and 7.68 ppm; E, single-frequency off-resonance decoupled by irradiation at δ_H = 10 ppm.

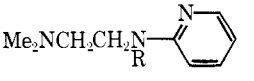


VIII

The resonances of the pyridyl unit are assigned by comparison with the chemical shifts of the analogous carbons in 2-aminopyridine[10] (IX) and in antihistamine drugs[11] (X).



IX



X

The C_4 and $C_{1'}$ resonance signals are too close to each other (152.8 and 152.5 ppm) to be distinguished directly. These two carbons are both quaternary, which rules out hydrogen–deuterium replacement as a method for their differentiation. However, based on the experience in sulfathiazole,

Table II. ^{13}C NMR Chemical Shifts[a] in Alkaline Aqueous Solution

Carbon	I	III	IV	V	VI	VII	VIII
1	136.9	130.0	137.2	131.9	132.1	132.1	131.9
2	127.1	128.7	127.8	128.5	128.8	129.5	128.4
3	115.6	115.2	120.2	115.2	115.2	114.7	115.3
4	149.6	150.6	140.8	150.4	150.5	150.2	150.2
1'		170.1	169.8	163.1	163.2	163.2	159.3
3'		136.7	136.6	158.4	169.4	168.0	147.9
4'		110.6	110.9	112.4	112.3	111.5	115.5[b]
5'				158.4	157.8	168.0	138.5
6'							114.8[b]
CH_3					23.5	23.0	

[a] Parts per million downfield from Me_4Si. [b] These assignments may be reversed.

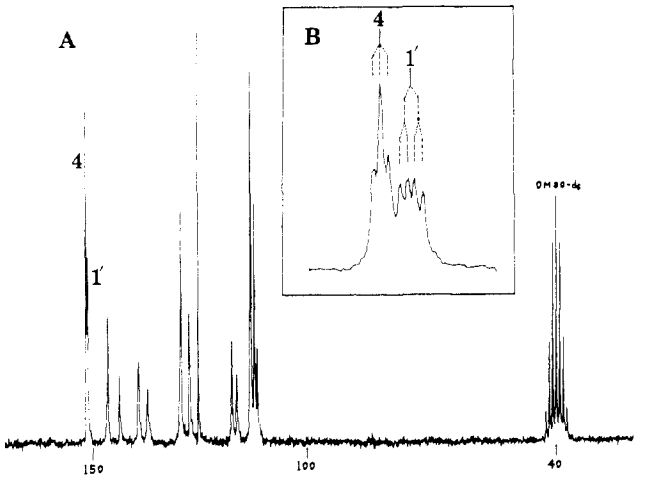
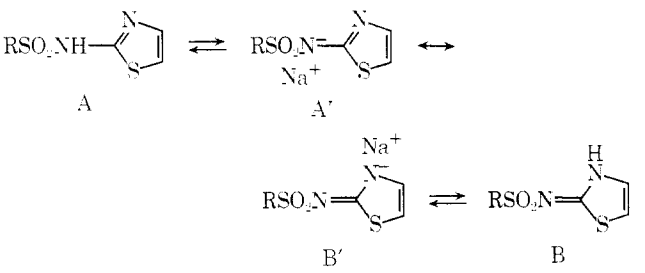


Figure 2. ^{13}C NMR spectrum of sulfapyridine in DMSO-d_6, single-frequency decoupled by irradiation at δ_H = 6 ppm: A, normal scale; B, expanded scale.

the single-frequency proton decoupled C_4 signal should appear as a triplet because the two C_2 protons are identical, whereas the $C_{1'}$ signal should become a doublet of doublets, since $J_{red.}$ ($C_{1'}NC_{3'}H$) $\neq$ $J_{red.}$ ($C_{1'}C_{6'}C_{5'}H$) due to the nonequivalence of the $C_{3'}$ and $C_{5'}$ protons ($\Delta f_{3'\text{-}H} \neq \Delta f_{5'\text{-}H}$). The single-frequency decoupled (irradiate at δ_H = 6.0 ppm) spectrum indeed indicates these splittings (Figure 2) and therefore the 152.8- and 152.5-ppm peaks can be unambiguously assigned to C_4 and $C_{1'}$, respectively.

The spectral data in alkaline aqueous solutions are summarized in Table II. The chemical shifts were assigned by a similar approach as described above. The firm assignments of sulfanilamide (I) provide the basis for the signal designation of the sulfonamide unit of all other drugs. The ^{13}C resonances of the thiazole portion of sulfathiazole (III) were definitively assigned by selective proton decoupling experiments. The downfield shifts of the carboxylic carbonyl carbon and its α-carbon and β-carbon in going from the acid to its anionic form, which result from the through-space interaction of the negative charge[12] and the change of C–H bond polarization,[13] are expected to be 4.8, 3.5, and 1.6 ppm, respectively.[12] Therefore the 181.2- and 174.3-ppm peaks are assigned to C_8 and C_5 of sulfasuxidine (IV), respectively, and the 33.4- and 32.8-ppm signals can be assigned to C_6 and C_7. The resonance assignments of the pyrimidyl derivatives are very straightforward on the basis of the previous assignments of the spectra in dimethyl sulfoxide solution. The $C_{1'}$ and C_4 signals are well separated; thus there is no ambiguity in this case. However, $C_{4'}$ and $C_{6'}$ cannot be clearly distinguished.

The chemical shift change of the α-carbon of the sulfonamide group from the neutral form to the anion could be ascribed to the change of excitation energy[14] and/or bond order[15] by analogy to the nitrogen heterocycles. The change of electron density of the meta carbons and the para carbon of the sulfanilamide moiety probably accounts for the meta-downfield shift and the para-upfield shift.[2] However, the chemical shift changes of the thiazole unit are somewhat unusual, particularly the large downfield shift of the $C_{3'}$ resonance and the fact that little change is seen in the $C_{1'}$ signal. One of the plausible explanations is that this might be due to the solvent perturbation of the tautomeric equilibrium in solution. It seems likely that the thiazole anion predominantly exists in the B′ form, which would also account for the weaker downfield shift of the C_1 signal (ca. 2 ppm) in reference to the other compounds (ca. 6 ppm).



Experimental Section

The NMR spectra of about 1 M solutions of the compounds in deuteriodimethyl sulfoxide (DMSO-d_6) and 2 N NaOD solution were obtained in 10-mm (^{13}C NMR) and 5-mm (^1H NMR) spinning tubes. Tetramethylsilane (Me_4Si) was used as internal reference for ^1H NMR spectra. The ^{13}C resonances of deuteriodimethyl sulfoxide and methanol served as internal reference for ^{13}C NMR spectra and conversion to the Me_4Si scale involved the following corrections: δ (Me_4Si) = δ (DMSO-d_6) + 39.6 ppm; δ (Me_4Si) = δ (MeOH) + 49.3 ppm. The instrument employed was a Jeol PFT-100 spectrometer operating at 23.5 kG, interfaced with a Jeol EC-100 Fourier tranform computer with 20K memory. The spectra were recorded at ambient temperature using a deuterium lock. All proton lines were decoupled by a broad band (2.5 kHz) irradiation from an incoherent 99.99-MHz source. The chemical shifts were measured for 5000-Hz sweep width. The typical pulse width was 10 μsec, and the repetition time between pulses was 3.0 sec.

All sulfonamide drugs were USP grade materials. They were used without further purification.

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Antiinflammatory β-Arylamidoacrylic Acids

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A series of 34 β-arylamidoacrylic acids was prepared and examined for antiinflammatory activity. These compounds are vinylogous carbamic acids, and several displayed activity equal to phenylbutazone in the rat pleural effusion model. Highest activity was associated with structures bearing halogen and cyano substituents. Amides were inactive.

We became interested in the title compounds for two reasons. They appear as partial structures in a number of antiinflammatory compounds such as the fenamates and the related benzamido benzoic acids.[1,2] And they satisfy the rudimentary structural requirements suggested for certain nonsteroidal antiinflammatory acids: an aryl group attached to a nonbasic nitrogen atom that is separated from the carboxyl group by one or two atoms.[3,4] Because of its simplicity, we felt that the structure of these compounds might be close to the minimum geometry and constitution necessary for such activity.

Carbamic acids are unstable, they decompose spontaneously with loss of carbon dioxide. The few that are known are extensively stabilized by hydrogen bonding.[5] Since double bonds transmit the electrical effects causing this instability, there was some doubt that vinylogous carbamic acids would be stable enough to be useful, even though one of them had been casually characterized earlier.[6] Nevertheless, when prepared these acids turned out to be stable to all but high temperatures and strong acids. They all decarboxylate at the melting point.

Chemistry. The arylamidoacrylic acids III were prepared as outlined in Scheme I (see Table I for details). The starting β-aminoacrylate esters I were made from the appropriate β-keto esters in the usual way.[7] Ethyl esters were preferred but methyl and *tert*-butyl esters were used when necessary. The acylation of the β-amino esters to give the β-amido esters II (see Table II for details) was uneventful except when the starting β-amino ester possessed an α-hydrogen atom (I, R_2 = H). In these cases the reaction proceeded to give both an N-acylated product (II, R_2 = H) and a C-acylated product (IV). The isomer ratio varied according to the reaction conditions but it was roughly unity for reactions in ether at room temperature. The isomer mixtures were easily separated by fractional crystallization or column chromatography on alumina or Florisil.

The ^{1}H NMR spectra of the N-acylated isomers displayed the vinyl proton at R_2 as a singlet in the range 290–310 Hz ($CDCl_3$). This peak was absent from the spectra of the C-acylated isomers. The infrared spectra of the C-acyl-