Registry No.—1, 52154-83-3; 2, 52154-84-4; 3, 65437-13-0; 4, 65392-50-9; 4', 65392-49-6; 6, 2826-19-9; 8, 65392-48-5; *endo*-dicyclopentadiene, 1755-01-7; nonbornene, 498-66-8.

References and Notes

(1) (a) This paper was presented in part at the 8th Western Regional Meeting of the American Chemical Society, San Francisco, Calif., October 1972; (b) NSF Undergraduate Research Participant, Summer, 1972; (c) MBS trainee, 1975.
(2) See, for example: O. L. Chapman and G. Levy, "Organic Photochemistry", Vol. 1, Marcel Dekker, New York, N.Y., 1967, pp 283–321; P. E. Eaton, *Acc. Chem. Res.*, **1**, 50 (1968); P. de Mayo, *ibid.*, **4**, 41 (1971).
(3) H. Prinzbach, *Pure Appl. Chem.*, **16**, 17 (1968); H. Prinzbach and W. Auge, *Angew. Chem., Int. Ed. Engl.*, **8**, 209 (1969), and references contained therein.
(4) D. R. Paulson, F. Y. N. Tang, and R. H. Sloane, *J. Org. Chem.*, **38**, 3967 (1973).
(5) K. Alder and G Stein, *Justus Liebigs Ann. Chem.*, **485**, 223 (1931).
(6) A. J. Durbetaki, *J. Org. Chem.*, **26**, 1017 (1961).
(7) J. Meinwald, S. S. Labana, L. L. Labana, and G. H. Wahl, Jr., *Tetrahedron Lett.*, 1789 (1965); K. Tori, K. Kitahonoki, Y. Takano, H. Tonida, and T. Tsuji, *ibid.*, 559 (1964).
(8) R. Wilder, C. Culberson, and G. T. Youngblood, *J. Am. Chem. Soc.*, **81**, 655 (1959).
(9) P. v. R. Schleyer, M. M. Donaldson, R. D. Nicholas, and C. Cupas, *Org. Synth.*, **42**, 8 (1962).
(10) A. Padwa and W. Koehn, *J. Org. Chem.*, **38**, 4007 (1973).
(11) P. D. Bartlett, G. N. Fickes, F. C. Haupt, and R. Hegelson, *Acc. Chem. Res.*, **3**, 177 (1970).
(12) R. R. Sauers, W. Schinski, and M. M. Mason, *Tetrahedron Lett.*, 4763 (1967), and references contained therein.
(13) R. Srinivasin and K. A. Hill, *J. Am. Chem. Soc.*, **88**, 3765 (1966).
(14) H. D. Scharf, *Tetrahedron*, **23**, 3057 (1967).
(15) W. E. Falconer, J. H. Knox, and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 782 (1961); T. Berces and A. F. Trotman-Dickenson, *ibid.*, 4281 (1961).
(16) G. O. Schenk and R. Steinmetz, *Chem. Ber.*, **96**, 520 (1963).
(17) D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Am. Chem. Soc.*, **87**, 2569 (1965).

Nuclear Magnetic Resonance Spectroscopy. Carbon-13 and Nitrogen-15 Spectra of the Penicillins and Cephalosporins

Jonathan W. Paschal and Douglas E. Dorman*

The Lilly Research Laboratories, Indianapolis, Indiana 46206

Puliyer R. Srinivasan and Robert L. Lichter

Department of Chemistry, Hunter College of the City University of New York, New York, New York 10021

Received September 1, 1977

^{13}C and ^{15}N NMR spectra of a selection of penicillin and cephalosporin antibiotics are reported and evaluated. The ^{13}C data seem in broad accord with the present theory of ^{13}C chemical shifts. ^{15}N chemical shifts are complicated by solvent effects, and correlations with structure are frequently difficult to recognize. While ^{15}N chemical shifts show no obvious relationship to biological activity, some correlations are possible in the case of ^{13}C.

The contributions of nuclear magnetic resonance (NMR) spectroscopy to studies of the structure and conformations of penicillins and cephalosporins have been many and varied.[1] Because of the relative simplicity of these molecules, routine ^1H NMR spectra usually suffice to elucidate their structures. Nuclear Overhauser enhancement (NOE) measurements provide further information regarding configuration and conformations in these systems.[1] In the rare cases wherein ^1H NMR spectroscopy fails to distinguish structural possibilities, the ^{13}C NMR spectra can be used.[2] As part of a general exploration of the applicability of ^{15}N NMR spectroscopy to organic and biological chemistry, we have measured the ^{15}N NMR spectra of a number of penicillin and cephalosporin derivatives.[3] The purpose of the present paper is to report these results and to provide additional data regarding ^{13}C chemical shifts in these systems.

Experimental Section

Spectra were measured at natural abundance on JEOL PFT-100 multinuclear spectrometers, using the SD-HC heteronuclear decoupler. Data were collected into the JEOL EC-100 computer. Operating frequencies were 10.09 MHz for ^{15}N and 25.03 MHz for ^{13}C spectra. ^{15}N spectra were accumulated over a 4-KHz sweep width in 8 K of memory, using 15–25° tip angles and 1.2–2.0 s repetition rates. Depending on sample, accumulation times ranging from 6 to 16 h were required to obtain satisfactory signal-to-noise ratios. Data were collected and transformed under conditions which would be expected to lead to 0.7–2.0 Hz line broadening.

Whenever possible, spectra were measured in neutral or near-neutral aqueous solutions. Enough D_2O (10%) was added to provide internal lock. Carbon chemical shifts were measured relative to internal 1,4-dioxane and adjusted to the Me_4Si scale by the relation: $\delta_C(Me_4Si) = \delta_C(\text{diox}) + 67.4$. ^{15}N chemical shifts were measured relative to external NH_4Cl (2.9 M) dissolved in 1 M HCl.

^{13}C and ^{15}N resonance assignments are based on chemical shifts,[4] off-resonance and single-frequency decoupling experiments,[4] relative peak heights,[3] and partial exchange experiments.[5]

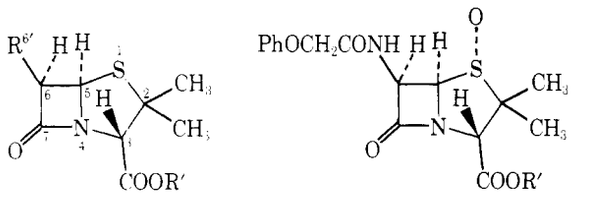
Results and Discussion

Penicillins. The structures of the penicillins studied in this work appear in Figure 1. ^{15}N chemical shift data for both the free antibiotics and their methyl esters are presented in Table I. Inasmuch as the ^{15}N spectra of the free antibiotics were measured in aqueous solutions at pH ~6, the carboxylic acid may be assumed to be fully deprotonated.

For the free penicillins, the lactam resonance appears at about 144 ppm. In penicillin V α-sulfoxide, the N(4) resonance is substantially shielded (125.9 ppm), as might be expected from the usual γ effect of oxygen in ^{15}N chemical shifts.[6,7] Because the rigid penicillin nucleus prevents the oxygen from approaching N(4) closely, this shielding cannot be due to a steric effect. This is in agreement with other studies[4b] which show that steric interactions are not essential to the shielding effects of γ heteroatoms.

Except for the example of hetacillin, the lactam nitrogen chemical shifts in these penicillins appear to be relatively insensitive to changing substitution at N(6'). The case of hetacillin is unique in that N(6') is incorporated into a lactam ring which bears bulky substituents. In those β lactams which have been studied by x-ray crystallography,[8] the amide N–H has been shown to be projected above the β-lactam ring. In an

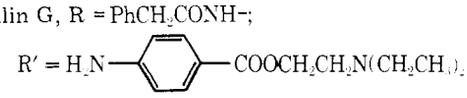
0022-3263/78/1943-2013$01.00/0



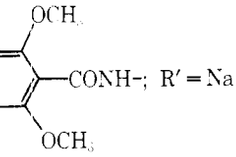
penicillin V α-sulfoxide

Penicillin G, R = $PhCH_2CONH-$; R′ = K

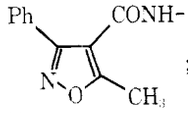
Procaine penicillin G, R = $PhCH_2CONH-$;



Penicillin V, R = $PhOCH_2CONH-$; R′ = Na

Methicillin, R =  R′ = Na

Ampicillin, R = $PhCH(NH_2)CONH-$; R′ = Na

Oxacillin, R =  ; R′ = Na

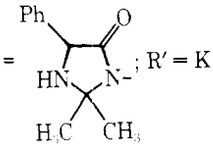
Hetacillin, R =  ; R′ = K

Figure 1. Structures of penicillin derivatives studied in this work.

Table I. ^{15}N-NMR Chemical Shifts in Penicillin Derivatives

Penicillin derivatives	Registry no.	N(4)	N(6′)	Other	Solvent
Methyl esters					
Penicillin G	653-89-4	134.3	85.1		C_6D_6
Penicillin V	2315-05-1	134.8	80.5		1,4-Dioxane
Penicillin V α-sulfoxide	25547-92-6	117.3	78.9		1,4-Dioxane
Methicillin	22668-52-6	136.8	83.4		C_6D_6
Ampicillin	65404-78-6	135.4	78.2	1.1	C_6D_6
Oxacillin	27605-29-4	135.4	87.7	274.9	CH_2Cl_2–C_6D_6
Hetacillin	4052-65-7	124.9	78.4	35.8	CH_2Cl_2–C_6D_6
Salts					
Penicillin G, K	113-98-4	143.7	90.7		H_2O
Penicillin G, K		142.6	86.6		Me_2SO
Penicillin G, procaine	54-35-3	137.1	87.3	45.2, 25.9	Me_2SO
Penicillin V, Na	1098-87-9	143.1	85.5		H_2O
Penicillin V α-sulfoxide, Na	65338-34-3	125.9	82.5		H_2O
Methicillin, Na	132-92-3	144.5	95.8		H_2O
Ampicillin, Na	69-52-3	144.5	87.6	9.6	H_2O
Oxacillin, Na	1173-88-2	144.1	92.1	262.3	H_2O
Hetacillin, K	5321-32-4	132.1	86.0	48.6	H_2O

analogous conformation, the geminal dimethyl group of the side chain of hetacillin would be expected to interact sterically with the thiazolidine ring and its substituents. We suggest that conformational differences resulting from these interactions account for the unusual ^{15}N chemical shifts in hetacillin.

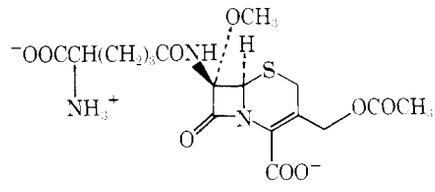
In the methyl esters of these penicillins, the lactam nitrogens are seen to come into resonance approximately 8–10 ppm higher field than in the parent antibiotics. The lactam resonance of procaine penicillin G also occurs at unusually high field. These changes are likely due to differences in the charge on the adjacent carboxylate group, in analogy to the observed changes at the β carbon of carboxylic acids.[9] In cases wherein this charge is present, the lactam nitrogen comes into resonance at relatively lower field than when the charge is absent, as in the esters, or dispersed through ion pairing, as in procaine penicillin G.

As might be expected, the chemical shift of N(6′) is much more dependent upon the identity of the amide. Some of the observed chemical shift differences can be interpreted in the light of our present understanding of ^{15}N chemical shifts. Thus, the upfield positions of N(6′) in penicillin V and ampicillin relative to penicillin G most probably result from the γ heteroatoms included in the side chains of these derivatives.[7] Other changes in the chemical shift of N(6′) are not easily explained in terms of the present theory of ^{15}N chemical shifts. Thus, the effect of the sulfoxide oxygen of penicillin V sulfoxide relative to the parent antibiotic does not correlate well with the δ effect observed in other systems;[7,10] possibly this relatively shielded position of the N(6′) resonance of the sulfoxide results from increased electronegativity[7] of the γ substituent (i.e., sulfoxide vs. sulfide). Also, the N(6′) resonances of methicillin and oxacillin are deshielded relative to penicillin G; this is opposite the shielding effect usually observed in amides in which the carbonyl is in conjugation with an aromatic group.[6] Finally, the amide nitrogen of hetacillin comes into resonance slightly upfield of that of ampicillin, even though the former has two additional β substituents. In ^{15}N chemical shifts, the β effect has been found to be strongly deshielding in nature.[6,7] The discrepancy here is likely due to the fact that N(6′) in hetacillin is incorporated into a lactam, making direct comparison with the other analogues impossible.

The chemical shifts of the amide nitrogens of the methyl esters are all shielded relative to the free penicillins, the shift differences ranging from 3.6 ppm (penicillin V α-sulfoxide) to 12.4 ppm (methicillin). Most of these differences can be ascribed to solvent effects (vide infra).

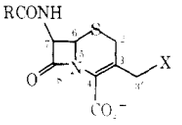
Cephalosporins. In Table II are gathered the ^{13}C and ^{15}N chemical shift data for the cephalosporins examined in this study. Because the cephalosporin nucleus has two sites of substitution (C-3′ and N-7′), it was considered likely that the ^{15}N chemical shifts would vary over a greater range than observed for the penicillins. Accordingly, some effort was made to standardize the conditions of measurement, and all the data shown in Table II were obtained from the carboxylate salt of the cephalosporanic acid dissolved in aqueous solutions at pH values between 4 and 7. In a separate study,[11] it was determined that the ^{13}C NMR spectrum of cephalosporin C (**8**) was invariant in this pH range, and this was assumed to obtain also for the ^{15}N chemical shifts.

Compounds **1** through **8** differ only in the structure of the amide substituent, R. It is obvious that throughout most of this series, the ^{13}C NMR spectrum is essentially insensitive to this variation. Introduction of a methoxyl group at carbon 7 (**9**) leads to the expected large changes in the chemical shifts of the resonances of carbons 7 (α effect) and 6 (β effect).[4a] The upfield shift at C(8) parallels that associated with α haloge-



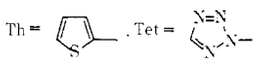
9

Table II. $^{13}C^{a}$ and $^{15}N^{b}$ Chemical Shifts in Cephalosporins

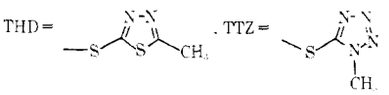


	Registry no.	R[c]	X[d]	C(2)	C(3)	C(3′)	C(4)	4-CO_2^-	N(5)	C(6)	C(7)	N(7′)	CO	C(8)
1	27267-35-2	H	OAc	26.3	117.1	64.9	132.3	169.1	129.3	57.6	58.5	89.6	165.4[e]	165.5[e]
2	32178-86-2	CH_3	OAc	26.3	116.9	65.0	132.3	169.2	129.7	58,0	59.9	87.5	175.5	165.9
3	859-07-4	$PhCH_2$	OAc	26.3	116.9	65.0	132.3	169.2	129.7	58.2	60.0	86.7	176.0	165.5
4	10390-44-0	$PhOCH_2$	OAc	26.3	117.0	65.0	132.3	169.1	129.3	58.0	59.4	81.1	172.7	165.1
5	27910-26-5	PhC(OH)H–	OAc	26.3	116.8	65.0	132.3	169.0	129.6	58.1	59.6	81.4	176.2	165.2
6	153-61-7	$ThCH_2$	OAc	26.3	116.9	65.0	132.3	169.1	129.3	58.1	60.0	85.5	174.8	165.4
7	43141-96-4	$TetCH_2$	OAc	26.3	117.2	65.0	132.3	169.2	129.1	57.8	60.0	83.5	168.2	165.1
8	47580-44-9	AAA	OAc	26.3	116.9	65.0	132.3	169.3	129.4	58.0	59.9	87.1	177.3	165.7
9	32178-82-8	7-OMe, AAA	OAc	26.5	116.7	64.8	132.4	168.8	n.a.[f]	63.4	95.7	n.a.[f]	178.1	161.1
10	34691-02-6	$ThCH_2$	H	29.3	123.2	19.4	127.5	170.6	n.a.	57.7	59.6	n.a.	174.6	165.0
11	5935-65-9	$ThCH_2$	OH	26.2	122.1	61.8	130.3	169.8	n.a.	58.2	59.9	n.a.	174.9	165.5
12	26722-85-0	$ThCH_2$	SCH_3	27.7	120.9	36.1	130.4	169.5	n.a.	58.6	59.8	n.a.	174.4	165.1
13	13057-93-7	$ThCH_2$	PYR	25.9	113.1	62.6	135.9	167.9	130.8	58.3	60.4	85.9	174.5	165.4
14	26970-95-6	$ThCH_2$	THD	27.7	119.1	38.7	131.9	168.4	n.a.	58.5	59.9	n.a.	174.3	165.3
15	33306-26-2	$TetCH_2$	THD	27.7	119.6	38.8	132.0	168.5	130.7	58.1	59.9	83.7	168.1	165.0
16	65338-32-1	PhC(OH)H–	TTZ	27.4	118.9	37.2	131.7	168.4	n.a.	58.2	59.5	n.a.	176.2	165.0
17	10209-11-7	$PhOCH_2$	H	29.3	123.4	19.4	127.6	170.4	n.a.	57.5	59.0	n.a.	172.3	164.7
18	27726-35-8	$PhC(NH_2)H$–	H	29.2	122.7	19.3	127.4	170.6	129.9	57.8	59.1	83.7	176.9	164.8

[a] In ppm from Me_4Si. [b] In ppm from NH_4Cl. [c] Abbreviations used: Ph = phenyl,



AAA = $HOOCC(NH_2)H(CH_2)_3$–. [d] PYR = pyridinium



[e] May be interchanged in assignment. [f] n.a. = not available.

nation of ketones.[4a] In analogy to the penicillins, variation of the structure of the amide substituent effects little change in the chemical shift of the lactam nitrogen. In fact, the variations in the N(5) chemical shifts in compounds **1–8** can be taken as a measure of the experimental error in these spectra.

Of greatest interest, however, are the chemical shift changes observed at the amide nitrogen, N(7′). Throughout the series of compounds **1–8**, the chemical shift of this nucleus varies over a range of approximately 8.5 ppm, thereby making it a sensitive measure of variations in the structure of R. The N(7′) chemical shift difference between **1** and **2** is small, consistent with the usually small differences between formamides and other amides.[6,7] The similarities in the chemical shifts of the N(7′) resonances of **2, 3,** and **8** indicate that in these systems, the γ effects of phenyl and methylene groups are very small. As before, however, the addition of a γ heteroatom brings about large shielding effects at the amide nitrogen, the largest changes being observed for the highly electronegative oxygen atoms of **4** and **5,** although the smaller changes observed for nitrogen and sulfur (**7** and **6,** respectively) must be considered experimentally significant. These results are again in broad accord with the usual correlation between the magnitude of the γ effect and the electronegativity of the γ substituent.[4b,7]

Compounds **6** and **10–14** form another series in which only one of the substituents on the cephalosporin nucleus is varied, this time the one attached to C(3′). Practical problems and deficiencies in supply prevent our reporting ^{15}N data for more than two compounds in this series. As might have been expected, the chemical shifts of the amide nitrogen and the three carbons of the β-lactam ring are relatively unchanged through this series. Somewhat more surprising is the small change in the chemical shift of N(5) for X equal to acetate and pyridinium (**6** and **13,** respectively). This point will receive further comment below.

The identity of X has a much larger effect on the chemical shifts of nearby carbons. Comparison of the spectra of this series shows that carbon 2 varies through a range of 3.4 ppm. Relating these chemical shifts to that of C(2) in **10** (X = H), it can be seen that these changes are due to γ substitution and that the magnitude of the shift is again related to the electronegativity of the atom attached to C(3′). When this atom is oxygen (**6, 11**) or positively charged nitrogen (**13**), the γ effect is approximately 3 ppm; for the less electronegative sulfur (**12, 14**), the shift is nearer 1.5 ppm.

Somewhat more dramatic effects are seen in the resonances of carbons 3 and 4. In **10** (X = H), the chemical shifts of these carbons differ by approximately 4 ppm. The addition of electronegative substituents at C(3′) increases this chemical shift difference, a phenomenon which is generally associated with increasing polarization of the π-electron clouds.[4a] For electronegative substituents such as acetate and pyridinium, the differences in the chemical shifts of carbons 3 and 4 exceed 15 ppm. Concurrent, but smaller, upfield shifts are seen to occur in the carboxylate (C-4′) resonances. The importance of this bond polarization to the activity of these compounds is suggested by the fact that the two compounds showing the greatest differences between the chemical shifts of carbons 3 and 4 (*cf.* **6** and **13**) are among the most successful cephalosporin antibiotics presently available commercially.

While there are presently rather few data available, it seems

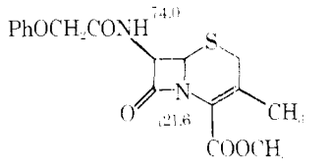
Table III. ^{15}N Data for the Acid and Sodium Salt Forms of 15

	N(5)	N(7′)	Other	Solvent
Salt[a]	130.7	83.7	204.9, 251.6	H_2O
Salt	130.8	82.1	205.7	Me_2SO
Acid	125.1	81.3	205.3	Me_2SO

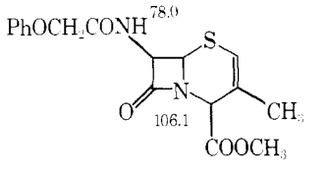
[a] Registry no. 65338-33-2.

evident from Table II that the range of chemical shifts shown by the lactam nitrogen of cephalosporins will be disappointingly small. Thus, throughout Table II, which includes compounds with X varying from H to pyridinium, the N(5) chemical shifts vary by less than 2 ppm. The contrast between this result and those discussed above for carbons 3 and 4 suggests that the effect of X is not efficiently transmitted *through* the carbon–carbon double bond to the lactam nitrogen.

When the double bond is removed from conjugation with this nitrogen, however, the chemical shift is strongly affected. Thus, the N(5) resonances of **19** and **20** differ by 15.5 ppm, a



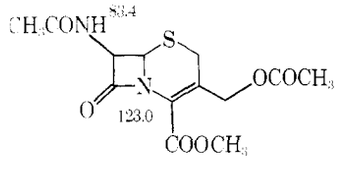
19



20

shift similar in both direction and magnitude to the chemical shift differences of the nitrogens of aniline and cyclohexylamine.[3,6,7] Also intriguing is the difference of 4 ppm in the amide nitrogen chemical shifts of **19** and **20.** This is a shift of surprising magnitude for a nitrogen so remote from the point at which the two structures differ. Most probably, the changes in these chemical shifts are influenced by the different interannular angles of the Δ^2- and Δ^3-cephem systems.[8]

In the penicillins, large changes were observed at both nitrogens in going from the free antibiotics in aqueous solution to the methyl esters in organic solvents. Comparison of the ^{15}N spectra of **2** and **21** provides a measure of the effect of the



21

analogous change in the cephalosporins. For the lactam nitrogen, this chemical shift difference is 6.7 ppm, which compares reasonably with the changes observed in the penicillins (7.2–9.4 ppm). For the amide nitrogen, the difference is 4.1 ppm, which again is similar to the previous examples. In an attempt to distinguish between the effects of differing charges on the carboxylate group and solvent effects, we measured the spectrum of **15** in both its acid and salt forms in dimethyl sulfoxide (Me_2SO) solution. The data in Table III show that the spectra of the salt of **15** in Me_2SO and water are quite similar, only the amide resonance being significantly different. This change in the chemical shift of N(7′), as well as that observed when **15** is converted to its acid form, is probably due to small changes in the solvation of the molecule. In contrast, the lactam nitrogen is seen to be shifted upfield by 5.7 ppm in the acid relative to the salt (Table III). This shift, which we believe results primarily from the change in charge on the carboxylate group, compares closely with the 6.7-ppm shift difference noted above for the lactam nitrogens of **2** and **21.** On the basis of these results, we believe that while the differences in the N(5) chemical shifts of the penicillins (Table I) can be ascribed primarily to ionization effects, the large changes in the amide nitrogen chemical shifts are largely due to solvent effects.

Conclusions

It is to be expected that ^1H NMR spectroscopy[1] will continue to be the predominantly used method in problems of structure elucidation and conformational analysis of the penicillins and cephalosporins. The greater expense of ^{13}C NMR spectroscopy in both time and money will probably result in its being reserved for rather specialized structure problems.[2,12] The present requirement for relatively large samples for ^{15}N NMR spectroscopy will make its use even more selective.

However, in structures with relatively few protons, especially at centers generally regarded as important to the biological activity, ^{13}C and ^{15}N NMR spectroscopy can provide detailed information regarding the electron distribution throughout the molecule. In some cases, there appears at least a broad correlation between carbon chemical shifts and the activities of the β-lactam antibiotics, as seen above in the cases of **6** and **13.** In a phenomenon as complex as biological activity, however, such correlations cannot be expected to be generally successful. At present, for example, there is nothing obvious in the ^{13}C or ^{15}N NMR spectra of **18** which can be correlated with its commerical success.

Many of the sources of ^{15}N chemical shifts are not well understood at present. It is apparent from the above discussion that generalizations derived from simpler systems do not necessarily apply to compounds of biological and commercial importance. Perhaps it is best to recognize the present empirical state of ^{15}N NMR spectroscopy, collecting data when possible, but without prejudicing ourselves about the type of answers we expect.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. In addition, the work at Hunter College was supported by the U.S. Public Health Service Grant GM-21148 from the Division of General Medical Sciences, the CUNY Faculty Research Award Program, the Research Corporation, and Eli Lilly and Company. Funds for the spectrometer were provided in part by NSF Instrument Grant GP-37025. We are grateful to Professor A. K. Bose for providing many of the samples used in this study.

References and Notes

(1) P. V. Demarco and R. Nagarajan in "Cephalosporins and Penicillins. Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, Chapter 8.
(2) S. Kukolja, N. D. Jones, M. O. Chaney, T. K. Elzey, M. R. Gleissner, J. W. Paschal, and D. E. Dorman, *J. Org. Chem.*, **40**, 2388 (1975).
(3) R. L. Lichter and D. E. Dorman, *J. Org. Chem.*, **41**, 582 (1976).
(4) (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972; (b) E. L. Eliel et al., *J. Am. Chem. Soc.*, **97**, 322 (1975).
(5) R. A. Newmark and J. R. Hill, *J. Magn. Reson.*, **21**, 1 (1976).
(6) R. L. Lichter in "Determination of Organic Structures by Physical Methods", Vol. 4, F. C. Nachod and J. J. Zuckerman, Ed., Academic Press, New York, N.Y., 1971, Chapter 4.
(7) R. L. Lichter and J. D. Roberts, *J. Am. Chem. Soc.*, **94**, 2495 (1972).
(8) R. M. Sweet in ref 1, Chapter 7.
(9) R. Hagen and J. D. Roberts, *J. Am. Chem. Soc.*, **91**, 4504 (1969).
(10) D. E. Dorman and J. W. Paschal, *J. Am. Chem. Soc.*, **98**, 6885 (1976).
(11) J. W. Paschal and D. E. Dorman, unpublished results.
(12) C. R. Harrison and P. Hodge, *J. Chem. Soc., Perkin Trans. 1*, 1772 (1976).