Organic Magnetic Resonance, 1976, Vol. 8, pp. 208 to 212.

Nitrogen NMR Spectroscopy: Application to some Substituted Pyrroles

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(Received 4 September 1975; accepted (revised) 25 November 1975)

Abstract—A series of ^{15}N labeled 2-acylpyrroles was prepared and the nitrogen and proton n.m.r. spectra obtained. ^{15}N chemical shifts for these compounds are reported for the first time. No correlation between the nitrogen chemical shift and any Hammett substituent constant could be found. No variation in $J(^{15}N—H)$ was observed for any compound with changes in solvent, temperature or concentration, ruling out any observable tautomeric equilibria for these systems. An increase in $J(^{15}N—H)$ with the addition of electron withdrawing groups indicates increasing polarization of the N—H bond and acidity of these molecules. Two and three bond ^{15}N couplings are also reported.

INTRODUCTION

THE UNUSUAL chemical behavior[1] as well as certain physical characteristics of the 2-acylpyrroles led some individuals[2–4] to postulate either hydroxymethylene or dimeric structures for these molecules. It is now recognized, however, that a more realistic interpretation of the reactions of these compounds is better developed in terms of the ready polarizability of the pyrrole nucleus. This assessment has been strongly supported in recent years by a number of physicochemical studies,[5] although information concerning these compounds derived from n.m.r. studies has been meager. This gap was due, in part, to the fact that the quadrupole relaxation of the ^{14}N nucleus frequently leads to increased relaxation rates of its spin coupled proton with consequent severe line broadening. Thus, detection and accurate chemical shift determinations have been difficult.

As the ^{15}N nucleus has no quadrupole moment, ^{15}N n.m.r. spectroscopy can be an attractive method for overcoming the difficulties of line broadening and can provide more information about the molecular structure of these heterocycles. Additionally, nitrogen n.m.r. spectroscopy can provide information concerning the electronic structure and hybridization of nitrogen, the mechanism of spin–spin coupling, the site of protonation of nitrogen compounds, the effect of protonation on chemical shifts and the rates of proton exchange at nitrogen.[6] However, examples involving application of heteronuclear n.m.r. spectroscopy to the study of pyrroles have been scarce, most of the work having been carried out on pyrrole or its alkyl derivatives.[7–9] Notable exceptions include a ^{14}N study[10] of hydrogen bond shifts in pyrrole, 2-acetylpyrrole and 2,5-diacetylpyrrole and a report[11] of ^{14}N spectra of some nitropyrroles. Nonetheless, a systematic study of some of the acyl derivatives of pyrrole by nitrogen n.m.r. spectroscopy has not yet been conducted. In view of this and other considerations, we have prepared a series of ^{15}N substituted acylpyrroles through a modification[12] of the Paal-Knorr synthesis[13] and investigated the proton and nitrogen n.m.r. spectra of these adducts.

RESULTS AND DISCUSSION

Heteronuclear chemical shifts

The ^{15}N and ^{14}N chemical shifts of the compounds investigated are given in Table 1. For comparison, values for the ^{15}N chemical shifts for 2-nitro- and 3-nitropyrrole derived from their ^{14}N analogs are also included. Difficulties in obtaining sufficient quantites of pure sample, precluded the use of ^{15}N 2- and 3-nitropyrrole. The validity of this approach is based on a study[14] which has demonstrated that there is no significant isotope effect on nitrogen shieldings. The chemical shifts are consistent with, though more accurate than, Saito's determination[10] of the ^{14}N chemical shifts for pyrrole, 2-acetylpyrrole and 2,5-diacetylpyrrole. They are also much more accurate than Lippmaa's values[11] for the nitropyrroles.

As molecular electronic environment is the origin of the magnetic shielding of a nucleus,[15] the chemical shift can provide a convenient means of studying differences in bonding and electronic environment in molecules. Several groups have been able to relate proton or heteronuclear chemical shifts with π-electron densities and/or Hammett substituent constants. A notable example[16] was the correlation of ^{19}F n.m.r. shielding parameters for *meta* substituted fluorobenzenes with σ_I. Among the examples of ^{15}N chemical shifts used in this fashion is a good correlation[17] for some aniline derivatives with calculated π-electron densities at nitrogen over a wide range of substituents. A correlation[18] with substituted nitrobenzenes was also observed, but the effect on the π-electron density at nitrogen was much weaker.

Similar correlations for the compounds investigated here were not found. Although there appears to be a

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TABLE 1. NITROGEN CHEMICAL SHIFTS[a]

Compound	$\delta(^{15}N)$ ppm	$\delta(^{14}N)$ ppm
Methyl 5-nitropyrrole-2-carboxylate	−0·20	
Pyrrole	0	0
2-Nitropyrrole	(0·55)[b]	0·55
2-Formylpyrrole	0·89	
2-Acetylpyrrole	4·24	
3-Nitropyrrole	(4·84)[b]	4·84
Methyl pyrrole-2-carboxylate	5·53	
Methyl 4-nitropyrrole-2-carboxylate	7·60	

[a] Chemical shifts (in ppm) are reported relative to pyrrole. A positive value of the chemical shift indicates a shift downfield from pyrrole. The ^{15}N or ^{14}N chemical shift of pyrrole is 120·7 ppm downfield from the $[NH_4]^+$ ion: [H. Saito and K. Nukada, *J. Am. Chem. Soc.* **93**, 1072 (1971)]. The ^{15}N resonance frequency of pyrrole is 10·134384 MHz in a magnetic field where the ^1H resonance of TMS is exactly 100 MHz. Similarly, the ^{14}N resonance frequency of pyrrole is 7·224625 MHz. All solutions are in acetone-d_6.

[b] Derived value.

general trend in the chemical shifts as the electron demand of the substituent increases, several of the compounds are out of order. In particular, the parent and the compounds bearing the nitro group at the β-position are not in agreement. Therefore, any attempted correlation with any set of substituent constants for these compounds would not contain the parent of the series and would be meaningless. That no correlation is possible is of no surprise, as the correlations which have been successful usually involved *meta* or *para* substituted benzenes. These are compounds for which steric interactions are unimportant and for which anisotropic magnetic field effects from the substituent groups are negligible because of the remoteness of the group. As is often the case experimental values are not easily divided into their contributing terms. For this series of compounds, additional effects overwhelm that part of the chemical shift which is due only to π-electron density. This problem may perhaps be overcome by examination of substituent effects for pyrroles bearing groups only in the β-position and/or by placement of an alkyl blocking group on the nitrogen. We are presently investigating this question.

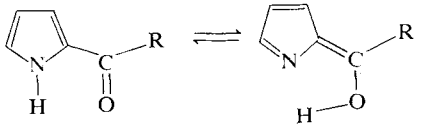
Coupling constants

The proton magnetic resonance spectra for the ^{15}N-pyrroles were recorded employing several solvents and in several instances as a function of temperature and of concentration. These spectra are summarized in Table 2. In all cases the N—H signal for the three monosubstituted compounds consisted of two apparent quartets. Decoupling experiments demonstrated that these 'quartets' result from a coupling in the range of 2·5 Hz to each of the ring protons. These results are in good agreement with published values.[19]

Solubility problems necessitated the use of a time averaging computer (CAT) to enhance the signals for the mixture of nitroesters in chloroform. The solubility problem was ameliorated with the use of acetone as solvent; however, it then became necessary to run the spectra at a lower temperature in order to slow down the N–H exchange. Assignment of the peaks to the correct isomer follows from the chemical shifts and the proton–proton coupling constants. The latter have been described[20] as 'sensibly' constant over a range of substituents, whereas the former is not always reliable as it can vary with the nature, location and proximity of the substituent. Simplification of the spectrum by *N*-proton deuterium exchange gave $J_{34} = 4{\cdot}35$, $J_{13} = 2{\cdot}70$ and $J_{14} = 2{\cdot}92$ for the 5-nitro-2-ester and $J_{35} = 1{\cdot}75$, $J_{13} = 3{\cdot}08$ and $J_{15} = 3{\cdot}26$ for the isomeric 4-nitro-2-ester. J_{34} and J_{35} are in close agreement with a previous determination;[20] all these coupling constants are generally as large as or larger than a set of values obtained[21] from several mono and disubstituted pyrroles.

Variations in the nature of the N—H bond, resulting from changes in hydrogen bonding or tautomeric equilibria, have been shown to be reflected in alterations in the N—H spin coupling. Axenrod[22] was able to assess the relative intramolecular hydrogen bonding abilities of various *ortho*-substituents in a series of anilines by comparing solvent dependent changes of $J(^{15}N—H)$. Similarly, Dudek and Dudek[23] demonstrated that for a series of Schiff bases, changes in $J(^{15}N—H)$ from temperature or solvent may be attributed to alterations in the proton residence time between oxygen and nitrogen (tautomeric equilibria).

The most striking feature of the data for these compounds is that the $^{15}N—H$ coupling constant remains fixed for each compound. No variation in $J(^{15}N—H)$ is observed with changes in solvent, temperature or concentration. Even in the more polar, better hydrogen bonding solvents, no change in J is observed. Also no real difference in J is observed for the three different monosubstituted acylpyrroles. It is clear that tautomeric equilibria (**1** ⇄ **2**) in these systems are not important and



1 **2**

no observable amount of the imine form is present. Furthermore, if tautomerization and not just proton exchange were important in the two nitroesters, the effect of lowering the temperature would be to freeze out the tautomers. In fact, no such freezing out takes place.

In contrast, Hughes and Rees[24] report a significant proportion of the enol tautomer for one compound in a series of 5-nitro-2-benzoylpyrroles. Based on our results, we question the likelihood of such a species. The presence of an enhanced [M − 17] peak in the mass spectrum cannot be taken as good evidence for an enol structure as one is dealing here with excited state and not ground state phenomena. Nor are we persuaded by their n.m.r. evidence which states that there is no coupling observed between the ring proton and H-1. A mixture of the 4- and the 5-nitroacylpyrroles shows very poor solubility in $CDCl_3$, the solvent used for their determination. Indeed, it is difficult to observe the 4-isomer at all. Thus, it is possible that the fine structure in the spectrum may have been an artifact. The coupling constants for H-1 and the ring protons for the two isomers have been reported above. We also note a reversal in their assignments for the chemical shift

TABLE 2. PROTON MAGNETIC RESONANCE DATA FOR ^{15}N-SUBSTITUTED PYRROLE DERIVATIVES[a]

Compound	Solvent	Temp. °C	δ(NH)	J(N—H)	δ(H-5)	δ(H-3)	δ(H-4)	δ(other)
2-Formylpyrrole	$CDCl_3$	27	10·79	98	7·19	7·01	6·34	9·50[b]
		40	10·74	98				
		50	10·63	98				
	$CDCl_3$[c]	27	9·90	98	7·12	6·98	6·33	9·50
	CCl_4	27	11·59	98	7·15	6·91	6·25	9·42
	CD_3COCD_3	27	11·13	98	7·24	7·01	6·32	9·55
	DMSO-d_6	27	12·08	97	7·21	6·99	6·28	9·49
		50	12·02	97				
		70	11·93	98				
2-Acetylpyrrole	$CDCl_3$	27	10·46	98	7·05	6·91	6·26	2·44[d]
		40	10·41	98				
		50	10·30	98				
	$CDCl_3$[c]	27	9·86	97·5	7·05	6·91	6·26	2·44
	CCl_4	27	11·29	98	7·01	6·79	6·12	2·40
	CD_3COCD_3	27	10·85	98	7·09	6·94	6·12	2·36
	DMSO-d_6	27	11·75	98	7·05	6·93	6·17	2·34
		50	11·73	98				
		70	11·63	98				
Methyl pyrrole-2-carboxylate	$CDCl_3$	27	9·70	98	6·91	6·91	6·23	3·85[d]
		40	9·67	98				
		50	9·59	98				
	$CDCl_3$[c]	27	9·30	97·5	6·92	6·92	6·25	3·85
	CD_3COCD_3	27	10·87	98	7·04	6·83	6·20	3·78
Methyl 5-nitropyrrole-2-carboxylate	$CDCl_3$	30	10·17	101·5	—	7·05	6·86	3·44[d]
	CD_3COCD_3	30		101[e]	—	7·12	6·91	3·85
Methyl 4-nitropyrrole 2-carboxylate	$CDCl_3$	30	9·64	100·3	7·77	7·38	—	3·92[d]
	CD_3COCD_3	30		100[e]	7·97	7·24	—	3·85
Pyrrole	$CDCl_3$	30	7·99	96	6·82[f]	6·26	6·26	—

[a] Chemical shifts are in ppm relative to internal TMS. *J* is given in Hz. Solutions are 10% w/v except where noted. [b] Aldehyde resonance. [c] 2% w/v solution. [d] Methyl resonance. [e] Coupling constant determined at −20 °C. [f] Also for H-2.

of H-3 and H-4 in their compounds. That these derivatives are benzoyl compounds and not the simpler acyl derivatives which we examined does not alter our comparison in that space-filling models show *ortho*-disubstituted benzenes are incapable of achieving simultaneous coplanarity between the carbonyl group and the benzenoid and heterocyclic rings. It is surprising to note that only the 5-nitro derivatives of the various compounds were obtained as previous workers[20] had consistently obtained equimolar amounts of the 4- and 5-nitro derivatives for several different acylpyrroles.

By analogy with ^{13}C—H coupling, Roberts *et al.*[6] have shown that a relationship exists between the amount of s character in the nitrogen bond orbital and the ^{15}N—H coupling constant. Application of that empirical relationship [%s = 0·43 J(^{15}N—H) − 6] to the coupling constants determined herein yields an increase in the % of s character with the addition of electronegative substituents (Table 3). This increase in s character in the hybrid molecular orbital as one and then two electron withdrawing groups are added to the ring manifests itself in an increase in the acidity of the N—H, evidence for which was noted earlier.[20] Although the coupling constant shows little or no dependence on the nature of the solvent, a substituent dependence is observed. As

TABLE 3. %S CHARACTER IN THE N—H BOND AS A FUNCTION OF J(^{15}N—H)

Compound	J(^{15}N—H)	%s Character
Pyrrole	96	35·28
2-Formylpyrrole	98	36·14
2-Acetylpyrrole	98	36·14
Methyl pyrrole-2-carboxylate	98	36·14
Methyl 4-nitropyrrole-2-carboxylate	100·3	37·13
Methyl 5-nitropyrrole-2-carboxylate	101·5	37·65

it has been shown[25] that the resonance delocalization and not the inductive effect of a substituent is primarily responsible for changes in J(^{15}N—H), we see here further evidence for the polarization of the N—H orbital through resonance interaction with the pyrrole substituents.

In Table 4, observed values of two and three bond ^{15}N coupling constants are presented for the several compounds studied. As expected, the presence of the π-system leads to an enhancement of the coupling constants in contrast to the typically smaller values[26] across saturated carbon atoms. The strong three bond coupling to the ring protons, comparable with that of ^2J is reasonable for a system in which the two groups are fixed in a *trans* relationship. The three bond ^{15}N—H coupling constant is slightly higher in the three monosubstituted pyrroles for H-4 than it is for H-3. H-3 is the proton which appears at lower field due to stronger deshielding by the substituent. However, no obvious relationship between any of these longer range constants and the various substituents is apparent.

It is also of interest to note here that the resonance signal for the aldehydic proton of 2-formylpyrrole is a doublet of doublets. As shown by decoupling experiments, this pair of doublets results from a 1·25 Hz coupling to H-5 and a 2·90 Hz coupling to the ^{15}N. No coupling to H-3, H-4 or H-1 is observed. These results confirm previous evidence[21] that this proton is coupled through the nitrogen to H-5 by the 'straightest zigzag path'[27] and that the carbonyl must be fixed in a *syn* geometry with respect to the N—H.

Proton chemical shifts

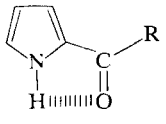
Chemical shift data derived from this study are consistent with previous work,[5,19] except that the greater precision in determining δ(N—H) enables one to observe

TABLE 4. LONG RANGE COUPLING CONSTANTS[a]

Compound	$^2J(^{15}N—H_5)$	$^3J(^{15}N—H_4)$	$^3J(^{15}N—H_3)$
Pyrrole[b]	4·52	5·39	5·39
2-Formylpyrrole	4·05	5·00	4·15
2-Acetylpyrrole	4·00	5·10	4·60
Methyl pyrrole-2-carboxylate	4·10	4·95	4·31
Methyl 4-nitropyrrole-2-carboxylate	3·45	—	5·05
Methyl 5-nitropyrrole-2-carboxylate	—	3·63	3·05

[a] All coupling constants are in Hz and are for chloroform solutions.
[b] Ref. 7, no solvent.

the changes in hydrogen bonds more clearly. Unlike the $J(^{15}N—H)$ coupling constants discussed earlier, such chemical shifts are extremely sensitive to changes in hydrogen bonding. The chemical shift of the N—H signal is a composite consisting of contributions from the resonances of nonbonded (free) molecules, intramolecularly hydrogen-bonded species (**3**) and molecules intermolecularly hydrogen bonded to the acyl group of a second molecule (**4**) or to the solvent (an intrinsic solvent dependence).



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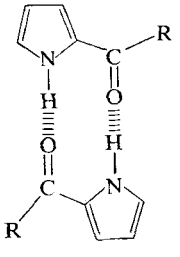

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As in most cases, significant shifts in the resonances of the bonded proton to lower field are expected with the formation of a hydrogen bond. In the polar solvents the situation is more complex, inasmuch as the solvents themselves can act as N—H acceptors. Among the hydrogen bonds which are possible, the strength of the linear hydrogen bond of the dimeric complex **4** is probably greater than that of the intramolecular bond **3**, in which the N—H acceptor is situated 90° relative to the N—H axis. The fraction of the latter species contributing to δ(N—H) cannot be very large. On dilution, there is a modest shift to higher field, representing a breakup of the intermolecular hydrogen bond and an increase in the number of free molecules. Were the intramolecular species important, dilution would have little effect on its contribution to the chemical shift. Lower field shifts might also be expected if there were a significant amount of **3** in solution. For example, the enolic hydrogen of the intramolecularly bonded acetylacetone appears at 15·5 ppm.[28]

Changes in the relative positions of the ring protons with changes in solvent are also observed although these shifts are very much smaller than for N—H. They too are the result of changes in the nature and strengths of the hydrogen bonds, which, in turn, give rise to variations in the shielding at the other positions. The chemical shifts reported here (Table 2) are consistent with previous studies[5,19] and confirm the point that the isotopic substitution of ^{15}N for ^{14}N has no effect upon the chemical shifts of the species studied.

EXPERIMENTAL

All melting points and all boiling points were not corrected. Gas liquid chromatography was carried out on an F & M Model 720 instrument using a 5 ft column of 20% SE-30 on 60/80 Chromosorb W. The i.r. spectra were determined with a Perkin-Elmer Model 137 i.r. spectrophotometer. Proton n.m.r. for the non-pyrrolic compounds were obtained with a Varian Model A 60 spectrometer and are reported in ppm downfield from internal TMS. All other proton n.m.r. spectra were obtained with a Varian Model XL-100 or HA-100 spectrometer. Samples were *c.* 10% w/v solutions unless specified otherwise. The variable temperature probe was calibrated in the usual fashion with ethylene glycol. 99·3 atom % ^{15}N-ammonium acetate was obtained from Merck and Company. As decarboxylation of the nitroester did not yield samples of 2- and 3-nitropyrrole (^{15}N) of sufficient purity for accurate spectral determinations, the ^{14}N analogs[29] of these compounds were utilized for this study.

All $^1H—\{^{15}N\}$ or $^1H—\{^{14}N\}$ heteronuclear double resonance experiments were performed on a Varian Model HA-100 spectrometer with the probe modified for such an experiment.[30] The decoupling power was provided by a Hewlett Packard Model 5100 B frequency synthesizer and Model 5110 B synthesizer driver. The 100 MHz radio frequency for proton resonance was obtained by mixing 20 and 30 MHz constant frequencies from the synthesizer to 50 MHz, which was amplified and finally doubled in the Model V-4311 r.f. unit. The decoupling frequency was read directly from the synthesizer. The accuracy of measurement was ± 1 Hz or better.

2-Formylpyrrole (^{15}N). A solution of 0·695 g (2·65 mmol) of 2-diethoxymethyl-2,5-diethoxytetrahydrofuran[31] and 0·198 g (2·57 mmol) of ^{15}N-ammonium acetate in 5 ml of glacial acetic acid was refluxed for 3 h under an argon atmosphere. The solution was diluted to 80 ml with water and then extracted with four 25 ml portions of ether. The combined extracts were washed with water, sat. $NaHCO_3$, sat. NaCl, and dried ($MgSO_4$), and evaporated *in vacuo* to a brown solid. Sublimation of the residue at 45°/0·3 mm gave 0·092 g (38%) of the pyrrole.

Methyl pyrrole-2-carboxylate (^{15}N). A suspension of silver oxide was prepared by the addition of 0·417 g (2·46 mmol) of silver nitrate in 3 ml of water to a stirred solution of 0·211 g (5·25 mmol) of sodium hydroxide in 3 ml of water. To the stirred suspension was added portionwise a solution of 0·12 g (1·26 mmol) of 2-formyl pyrrole (^{15}N) in 2 ml of 50% aqueous methanol. After the solution had been stirred for 1 h, it was filtered and the filter washed with 25 ml of hot water. The filtrate was cooled, extracted with 10 ml of ether and then neutralized with diluted HCl. Extraction of the aqueous solution with four 15 ml portions of ether, followed by drying (sat. NaCl, $MgSO_4$) the combined extracts and evaporation *in vacuo*, gave 0·3 g of solid. The solid was dissolved in 10 ml of methanol and 5 ml of ether and was treated with ethereal diazomethane until the color persisted. The solution was stirred at room temperature for 1 h and then evaporated *in vacuo*. Sublimation (55 °C/0·5 mm) of the residue gave 0·129 g (82%) of the ester.

2,5-Dimethoxy-2-(α,α-dimethoxyethyl)-2,5-dihydrofuran. 18·6 ml (0·33 mol) of bromine in 350 ml of methanol were added dropwise over 80 min to a rapidly stirred solution of 36·7 g (0·33 mol) of freshly distilled 2-acetylfuran[32] in 100 ml of absolute ether and 150 ml of dry methanol, while the temperature was maintained at −40 °C. After the addition of bromine, the orange solution was stirred for an additional 45 min while the solution warmed to −10 °C. The solution was cooled to −45 °C and ammonia was bubbled until the solution was basic. The solution was then stirred for 4 h while its temperature rose to room temperature. After filtration of the ammonium bromide and trituration of the salt with additional ether, the filtrate was evaporated *in vacuo* to a dark oil. Distillation at reduced pressure gave 8·5 g of recovered starting material and 24·3 g of higher boiling fractions. Redistillation (96 °C/8 mm) [Lit.[33] 112–113 °C/14 mm] of the later fractions gave 20·8 g (39% based on recovered starting material) of the dihydrofuran, homogenous by g.l.p.c.: n.m.r. (CCl_4) δ5·98–5·93 (m, 2H, vinyl CH), 5·41 (b, 1H, α-H), 3·43, 3·20 and 3·11 (3s, 12H, OCH_3) and 1·26 (s, 3H, CH_3).

2-Acetylpyrrole (^{15}N). A solution of 0·137 g (1·78 mmol) of ^{15}N-ammonium acetate and 0·490 g (2·23 mmol) of 2,5-dimethoxy 2-(α,α-dimethoxyethyl)tetrahydrofuran[33] in 5 ml of glacial acetic acid was refluxed for 2½ h under an argon atmosphere. The dark solution was diluted to 125 ml with water and the aqueous solution extracted with several portions of ether. The combined extracts were washed with water, sat. $NaHCO_3$, sat. NaCl, dried ($MgSO_4$) and evaporated *in vacuo*. Crystallization of the residue from hexane followed by sublimation (60 °C/0·2 mm) gave 0·071 g (37%) of the ketone.

Nitration of methyl pyrrole-2-carboxylate (^{15}N). A cold solution of 0·21 ml (0·280 g, 4·4 mmol) of fuming nitric acid in 1·5 ml of acetic anhydride was slowly added to a stirred solution of 0·101 g (0·802 mmol) of the ester in 2 ml of distilled acetic anhydride at −12 °C. The solution was stirred for an additional 30 min, whereupon it was poured into 50 ml of water, diluted to 75 ml and stirred until all the acetic anhydride had dissolved. Sodium bicarbonate was added until the solution was slightly basic. The aqueous solution was extracted with four 25 ml portions of ether and the combined extracts dried (Na_2SO_4) and evaporated *in vacuo*. Sublimation of the residue at 125 °C/0·25 mm gave 0·098 g (72%) of a mixture of the 4- and the 5-nitroesters.

Acknowledgements—The authors gratefully acknowledge the aid of Mr C. Strom of New York University for obtaining some of the spectra for this study and the generosity of Dr Hideo Kon, NIH, for a gift of the ^{15}N pyrrole. Gratitude is also extended to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

REFERENCES

1. H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Vol. 1, Akademische Verlag, Leipzig, 1934.
2. A. Angeli and L. Alessandri, *Atti. Accad. Naz. Lincei* **23**, 93 (1914).
3. G. Rastelli and A. Mingozzi, *Gazz. Chim. Ital.*, **55**, 549 (1925).
4. B. Emmert and K. Diehl, *Chem. Ber.* **64**, 130 (1931).
5. R. A. Jones, *Adv. Heterocycl. Chem.* **11**, 383 (1970).
6. J. B. Lambert, B. W. Roberts, G. Binsch and J. D. Roberts, in B. Pesce (Ed.), *Nuclear Magnetic Resonance in Chemistry*, Academic Press, New York, 1965, pp. 269–275.
7. E. Rahkamaa, *Mol. Phys.* **19**, 727 (1970).
8. D. Gagnaire, R. Ramasseul and A. Rassat, *Bull. Soc. Chim. Fr.* 415 (1970).
9. D. Herbison-Evans and R. E. Richards, *Mol. Phys.* **8**, 19 (1964).
10. H. Saito and K. Nukada, *J. Am. Chem. Soc.* **93**, 1072 (1971).
11. E. Lippmaa, M. Magi, S. S. Novikov, L. I. Khmelnitski, A. S. Prihodko, O. V. Lebeden and L. V. Epishina, *Org. Magn. Reson.* **4**, 153 (1972).
12. N. Elming and N. Clauson-Kaas, *Acta Chem. Scand.* **6**, 867 (1952).
13. E. Baltazzi and L. E. Krimen, *Chem. Rev.* **63**, 511 (1963).
14. E. D. Becker R. B. Bradley and T. Axenrod, *J. Magn. Reson.* **4**, 136 (1971).
15. G. A. Webb, in T. Axenrod and G. A. Webb (Eds.), *Nuclear Magnetic Resonance Spectroscopy of Nuclei Other Than Protons*, J. Wiley and Sons, New York, 1974, Chapter 4.
16. R. W. Taft Jr, E. Price, I. R. Fox, J. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Am. Chem. Soc.* **85**, 709 (1963).
17. T. Axenrod, P. S. Pregosin, M. J. Wieder, E. D. Becker, R. B. Bradley and G. W. Milne, *J. Am. Chem. Soc.* **93**, 6536 (1971).
18. W. Bremser, J. I. Kroschwitz and J. D. Roberts, *J. Am. Chem. Soc.* **91**, 6189 (1969).
19. T. J. Batterham, *NMR Spectra of Simple Heterocycles*, Wiley, New York, 1973, pp. 147–158.
20. K. J. Morgan and D. P. Morrey, *Tetrahedron* **27**, 245 (1971).
21. S. Gronowitz, A. Hornfeldt, B. Gestblom and R. A. Hoffman, *Ark. Kemi* **18**, 133 (1961).
22. T. Axenrod and M. J. Wieder, *J. Am. Chem. Soc.* **93**, 3541 (1971).
23. G. O. Dudek and E. P. Dudek, *J. Am. Chem. Soc.* **86**, 4283 (1963).
24. C. G. Hughes and A. H. Rees, *J. Med. Chem.* **16**, 574 (1973).
25. T. Axenrod, M. J. Wieder, G. Berti and P. L. Barili, *J. Am. Chem. Soc.* **92**, 6066 (1970).
26. T. Axenrod, in M. Witanowski and G. A. Webb (Eds.), *Nitrogen NMR*, Plenum Press, London, 1973, pp. 292–302.
27. C. N. Banwell and N. Sheppard, *Discuss. Faraday Soc.* **34**, 115 (1962).
28. E. D. Becker, *High Resolution NMR*, Academic Press, New York, 1969, pp. 23–4.
29. K. J. Morgan and D. P. Morrey, *Tetrahedron* **22**, 57 (1966).
30. H. J. C. Yeh, R. G. Tschudin, D. N. Lincoln and E. Lustig, *J. Magn. Reson.* **10**, 235 (1973).
31. J. Fakstorp, D. Raleigh and L. E. Schniepp, *J. Am. Chem. Soc.* **72**, 869 (1950).
32. A. L. Mndzhoian (Ed.), *Synthesis of Heterocyclic Compounds*, Vol. 4, Consultants Bureau, New York, 1959, p. 12.
33. J. T. Nielsen, N. Elming and N. Clauson-Kaas, *Acta Chim. Scand.* **9**, 9 (1955).