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ANISOCHRONISM OF DIASTEREOTOPIC GROUPS IN 1-ISOPROPYL- AND 1-ISOBUTYL-2-ACYL-1, 2-DIHYDRO- ISOQUINALDONITRILES

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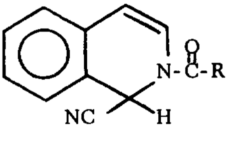
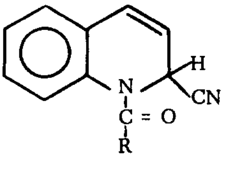
Recently much interest has been expressed in chemical shift differences of diastereotopic groups (1) . Halpern et. al. (2) and Kajtár and Radics (3) have demonstrated that steric bulk about the diastereotopic groups plays a role in determining the magnitude of this effect in isopropyl compounds. In this Letter we wish to report some preliminary results bearing on this point.

As part of a general program of studies designed to learn more about the stereochemistry of Reissert compounds, 2-acyl-1, 2-dihydroisoquinaldonitriles (I) and 1-acyl-1, 2-dihydroquinaldonitriles (II) , and their derivatives, we have prepared some 1-alkyl derivatives of I.

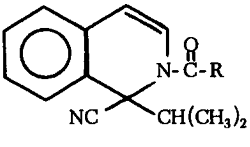
1-Isopropyl-2-acyl-1, 2-dihydroisoquinaldonitriles III a-c and IV (4) were prepared in good yields by reaction of the appropriate Reissert compound with sodium hydride and isopropyl bromide or iodide in dimethylformamide (5) . In the pmr spectra of these compounds the methyl protons are anisochronous (6),



I



II



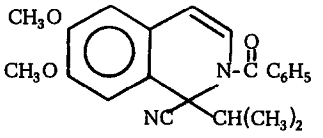
III a R = C_6H_5
b R = $C_6H_4CH_3$-o
c R = CH_3

i.e., have different chemical shifts. The magnitudes of these anisochronisms are relatively high (7), but are apparently insensitive to the nature of R. These results are summarized in Table I.

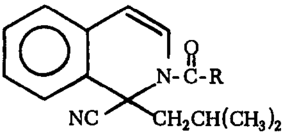
We have also synthesized compounds V a-c by the same procedure using isobutyl iodide. The spectra of these compounds exhibit the methylene protons as the AB portion of ABX systems. The methyl protons are also anisochronous. The extent of anisochronism of the methylene protons bears an inverse relationship to that of the methyl protons. And in contrast to the situation in the isopropyl compounds, the magnitudes of the differences are sensitive to the nature of R. These results are presented in Table II.

TABLE I (8)

Compound	Chemical Shifts (ν) of Methyl Protons		$\Delta\nu_{CH_3}$
III a	0.89	1.16	0.27
III b	0.87	1.18	0.31
III c	0.80	1.08	0.28
IV	0.94	1.24	0.30



IV



V a R = C_6H_5
b R = $C_6H_4CH_3$-o
c R = CH_3

TABLE II (8)

Compound	Chemical Shifts (ν) of Methylene Protons		$\Delta\nu_{AB}$	Chemical Shifts (ν) of Methyl Protons		$\Delta\nu_{CH_3}$
Va	2.23	2.50	0.27	0.78	0.94	0.16
Vb	2.17	2.73	0.56	0.84	0.87	0.03
Vc	1.98	2.57	0.59	0.76	0.78	0.02

Since these molecules are asymmetric, the methyl groups in compounds III, IV and V are diastereotopic as are the methylene protons in V. From inspection of molecular models of all possible conformations, it appears that steric hindrance is responsible for much of the anisochronism. This would be in keeping with previous suggestions for related structures (3, 9).

Since only one set of signals is observed for each of the protons, it appears that a single stable species or two or more rapidly exchanging species is/are present. In the systems reported herein nitrogen inversion, ring inversion and cis, trans amide isomerism are possible. The interplay of these factors, however, cannot be assayed confidently without further study. Currently, analogous compounds are under examination and studies of the solvent and temperature dependence of the spectra are in progress. The results of these efforts should allow more unambiguous conformational assignments for these compounds.

REFERENCES

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7. The largest reported anisochronism for isopropyl methyls to date is 0.73δ for a 1-isopropyl-tetrahydroisoquinoline derivative (ref. 3).
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