Reaction of 5-Diazouracils with Pyridines

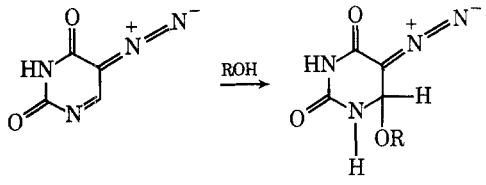
Brian T. Keen and William W. Paudler*

Department of Chemistry, The University of Alabama, University, Alabama 35486

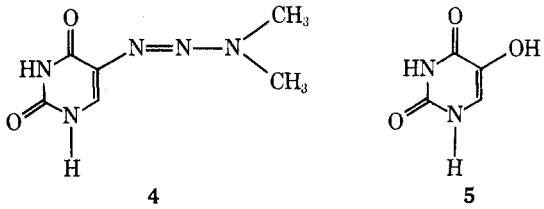
Received June 17, 1975

5-Diazouracil reacts thermally with pyridine, methyl isonicotinate, and 4-methoxypyridine to form 2- and 3-pyridyl derivatives of 5-substituted uracils. The ratio of 2:3 substituted pyridyluracils is the same for pyridine and methyl isonicotinate (1:2), while the 3-substituted pyridyluracil is the sole product when 4-methoxypyridine is used. A 5,5′-uracil dimer is a minor product in these thermal reactions. A uracil carbene is suggested as the intermediate in these reactions.

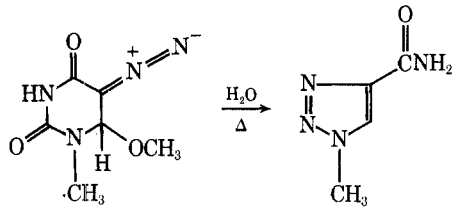
Some of the chemistry of 5-diazouracil (1) has been examined by Townsend and co-workers.[1-3] These researchers have shown that the compound has structure 1 and is readily covalently hydrated, or methanolated to form compounds 2 and 3. Compound 3 reacts readily with dimethylamine to form 5-(3,3-dimethyl-1-triazeno)uracil (4) and is converted to compound 5 by aqueous dilute hydrochloric acid.[4] The N-methylated compound 6, when heated in water, undergoes a ring contraction to the triazole 7.[3]



1 2, R = H 3, R = CH_3



4 5



6 7

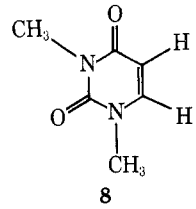
We now wish to describe the thermal reaction of 5-diazouracil (1), its covalently hydrated product (2), and its covalently methanolated derivative 3 with pyridine.

All three of these compounds afforded identical mixtures of isomeric materials (^{1}H NMR spectral and elemental analyses) analyzing for pyridyluracils and uracil.

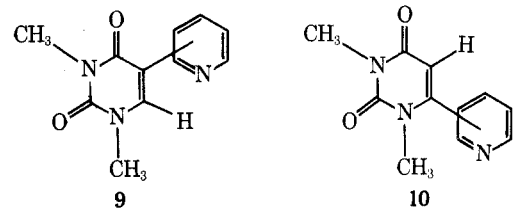
When the reaction was done under more concentrated conditions, an additional compound analyzing for a uracil dimer was obtained.

Since it was impossible to separate the mixture of pyridyluracils by either column or high-pressure liquid chromatography, the mixture was treated with diazomethane. The resulting compounds were separated by column chromatography to yield two different dimethyl pyridyluracils, along with some *N,N′*-dimethyluracil (8).

The latter compound was identified by a comparison with an authentic sample. The isomeric dimethyl pyridyluracils may have several possible structures. In order to establish the site of substitution on the uracil ring (9 or 10),

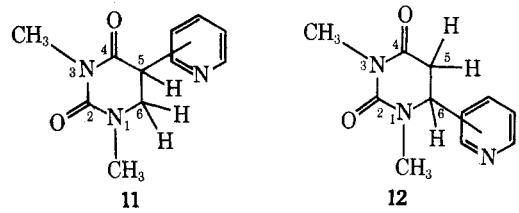


8



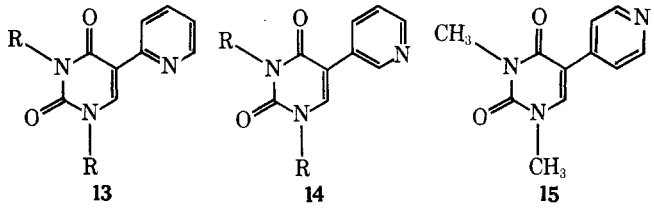
9 10

the compounds were catalytically reduced to dihydro derivatives (11 or 12). If the pyridine ring is at position 5 (structure 9) we would expect the H-5 proton in the dihydro derivative (11) to be subject to facile base-catalyzed H → D exchange, while, if the dihydro derivative 12 were formed, the two protons of C-5 would be subject to base-catalyzed H → D exchange. In fact, only one proton of the dihydro compounds (11a,b) is exchanged for deuterium in the presence of base. This exchange phenomenon is also observed in the dihydro compound 16 where the methylene protons



11 12

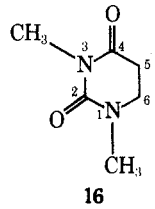
a, α-substituted pyridyl
b, β-substituted pyridyl



13 14 15

13: a, R = H; b, R = CH_3

14: a, R = H; b, R = CH_3



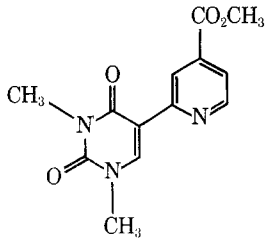
16

at C-5 are readily exchanged by deuterium in the presence of dilute base.[7] Consequently, substitution of the uracil ring at C-5 is confirmed. It now remains to establish the sites of substitution on the pyridine ring (structures **13b, 14b,** and **15** are possible). The ^{1}H NMR spectrum of the compound formed in higher yield (41%, **14b**) has a singlet at τ 2.55 which is no longer present as such in the dihydro derivative (**11b,** see Experimental Section). The remaining spectrum consists of an ABX system (τ 2.04, 2.67, 1.48) as well as a broad singlet at τ 1.34. The coupling constants in a 3-substituted pyridine, e.g., β-substituted picoline, are J_{45} = 6.8–9.1, J_{56} = 4.0–5.7, J_{24} = 0–2.5, and J_{46} = 0–2.5 Hz. The ABX pattern of the above compound has the following coupling constants: J_{45} = 8.0, J_{56} = 4.6, and J_{46} = 2.0 Hz. Thus, not only the multiplicity pattern, but also the coupling constants prove that the major pyridyluracil product obtained in these reactions has structure 14 (a 3-substituted pyridine).

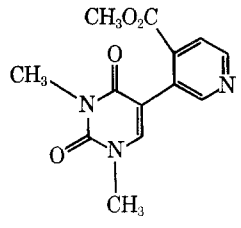
The other pyridyluracil (**13b**), formed in 21% yield, has a ^{1}H NMR spectrum composed of a singlet at τ 1.61 which is no longer present in the dihydro derivative (**11a,** see Experimental Section) and is consequently due to the uracil proton H_6 in structure **13b.** In addition to this singlet, an ABCD pattern is evident (τ 1.65, 2.30, 2.82, 1.50). The various coupling constants are J_{45} = 7.5, J_{56} = 5.0, J_{46} = 1.9, J_{34} = 7.8, J_{35} = 1.3, $J_{36'}$ = 1.2 Hz. A comparison of these values with those of α-substituted pyridines, e.g., α-picoline (J_{45} = 6.8–9.1, J_{56} = 4.0–5.7, J_{46} = 0–2.5, J_{34} = 6.8–9.1, J_{35} = 0.5–1.8, J_{36} = 0–2.3 Hz), along with the ABCD pattern itself, identifies the compound as an α-pyridyl derivative (**13b**).

In order to examine the effect that substituents on the pyridine ring have upon the isomer distribution, the thermal reactions of the diazouracil derivative **3** with 4-methoxy- and 4-carbomethoxypyridine were studied. Again, to facilitate isomer separation, the reaction mixture was treated with diazomethane and the resulting *N,N'*-dimethyl derivatives were examined.

In the case of the 4-methyl isonicotinate reaction, two isomeric products were again obtained. Their structures were established by an analysis of their ^{1}H NMR spectra in a manner similar to that described for the pyridyl isomers. Interestingly, while the overall yield of the isomers is less in the 4-methyl isonicotinate reaction, the relative percentages of the 2- vs. the 3-substituted isomers (1:2) (**17** and **18,**



17

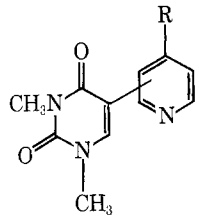


18

respectively) are the same as in the pyridine instance (**13** and **14**).

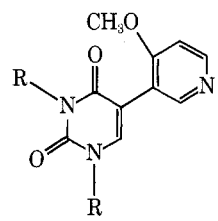
The reaction of **3** with 4-methoxypyridine and methylation of the resulting products with diazomethane afforded, in addition to uracil, a uracil dimer and two compounds, each giving an elemental analysis for $C_{12}H_{13}N_3O_3$. The compound formed in higher yield (**19**) has a ^{1}H NMR spectrum whose major salient feature is the presence of two fairly deshielded protons (τ 1.52, 1.63). The more deshielded of these protons is a broad singlet, while the other is part of an AB system (see Table I). A singlet at τ 2.68 is clearly due to the proton at C-6 of the uracil ring, and has a chemical shift similar to that proton in the 3-pyridyl derivative **14** (τ 2.55). Thus, we can conclude that this compound has structure **19.**

Table I
^{1}H NMR Data of Various Uracil Derivatives[a]



Compd[b]	Chemical shifts, τ					
	H_2	H_3	H_4	H_5	H_6	$H_{6'}$
2-Pyridyl, R = H (**13b**)		1.65	2.30	2.82	1.50	1.61
3-Pyridyl, R = H (**14b**)	1.34		2.04	2.67	1.48	2.55
2-Isonicotinate, R = CO_2Me (**17b**)		1.50		2.31	1.31	2.65
3-Isonicotinate, R = CO_2Me (**18b**)	1.06			2.27	1.36	1.58
3-(4-Methoxypyridyl), R = CH_3O (**19b**)	1.63			3.12	1.52	2.68
3-(*N*-Methyl-4-pyridonyl (**20**)	1.44			3.56	2.28	0.96

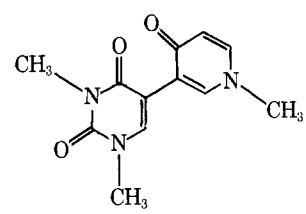
[a] Dilute solutions in $CDCl_3$. [b] The chemical shifts of the *N*-methyl protons are 6.50 ± 0.15. The pyridyl proton coupling constants are typical for pyridine derivatives.



19

a, R = H
b, R = CH_3

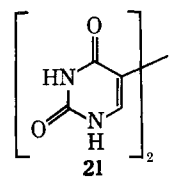
The compound, $C_{12}H_{13}N_3O_3$, formed in lower yield, could also be obtained by sublimation of compound **19.** Thus, one can strongly suggest that it has structure **20.**



20

This is confirmed by a comparison of its ^{1}H NMR spectrum with that of *N*-methyl-4-pyridone (see Table I).

The structure of the uracil dimer obtained in this reaction is readily established by the observation that the ^{1}H NMR spectrum shows the presence of only one highly deshielded proton (τ 1.55). Thus, the dimer must be a symmetrical one and have structure **21.**



21

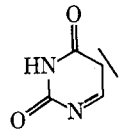
The yields of the various products for the different reactions are given in Table II.

Table II
Product Distribution of Various Pyridyluracils

Reagents	Substituent (R)	Compd	%	Substituent (R)	Compd	%
1, 2, or 3 + pyridine[a]	H	13b	21	H	14b	41
3 + 4-methyl isonicotinate	CO_2Me	17b	4	CO_2Me	18b	8
3 + 4-methoxypyridine	OCH_3		0	OCH_3[a]	19b + 20[a]	20

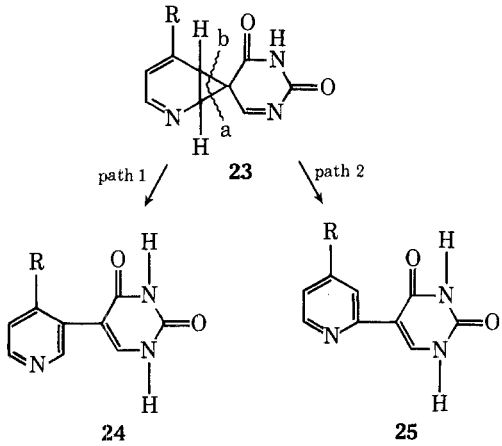
[a] A small amount of *O*-methylated products (10%) was also obtained. [b] Includes the percentage of *N*-methylpyridone derivative **20** obtained.

The formation of these pyridyluracils can, perhaps, be best explained by assuming the initial formation of the singlet, highly electrophilic carbene **22**.[6] Attack of this species



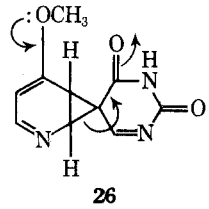
22

at the C_2–C_3 bond of the pyridines employed in this reaction would generate the intermediate cyclopropane **23**, which can form the 2- or 3-substituted pyridyluracil by either bond b or bond a cleavage, respectively, along with the



24 **25**

appropriate proton transfer to the sp^2-hybridized pyrimidine nitrogen. If R = OCH_3, the substituent will greatly facilitate formation of the 3-pyridyluracils (arrows in **26**). This is again in accordance with the experimental results.



26

On the other hand, if R = CO_2CH_3, a deactivation of the C_2–C_3 bond in pyridine toward attack by the carbene (**22**) is to be expected. Thus, the considerably decreased yield when methyl isonicotinate is used instead of pyridine is understandable. If R = CO_2CH_3 in structure **23**, the ratio of paths 1 vs. 2 should not be altered significantly in comparison to the case where R = H. Thus, the observation that the 2:3-substitution ratio is the same when methyl isonicotinate is used as it is in the pyridine instance is consistent with the experimental results.

Experimental Section

The 5-diazouracils **1** and **3** were prepared by the method of Thurber and Townsend.[1] The 5-diazouracil derivative **2** was prepared by recrystallization of compound **3** from 85° H_2O.[5] Pyridine was stored over type 4A molecular sieves.

Ultraviolet spectra were recorded on a Cary 14 spectrometer. Infrared spectra were determined on a Beckman Acculab 3 spectrometer, ^1H NMR spectra were recorded with a Varian HA-100, and mass spectra with a Hitachi Perkin-Elmer RMU-6M instrument. Melting points, determined with a Thomas-Hoover capillary melting point apparatus, are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga., and the Analytical Services Laboratory, Department of Chemistry, The University of Alabama.

Reaction of the Diazouracils 1, 2, and 3 with Pyridine. In a typical experiment 1.25 g (~7.5 mmol) of **1, 2,** or **3** was added to 40 ml of dry pyridine in a round-bottom flask equipped with a magnetic stirrer and reflux condenser. The reaction mixture was refluxed for 4 hr and allowed to come to room temperature. The pyridine was evaporated in vacuo and the residue was triturated with 50 ml of ether. The resulting solid was sublimed at 260° (0.2 Torr), recrystallized from boiling H_2O, and dried in vacuo to give 850 mg (60%) of the 5-pyridyluracils **13a** and **14a:** mp 330–335°; ir (Nujol) 1710 and 1670 cm^{-1} (amide C=O); uv (95% ethanol) λ_{max} 240 and 279 nm. Anal. Calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.09; H, 3.85; N, 22.18.

Preparation of 1,3-Dimethyl-5-pyridyluracils 13b and 14b. To 800 mg (4.2 mmol) of a mixture of 5-pyridyluracils **13a** and **14a** was added 25 ml of absolute CH_3OH. Excess CH_2N_2 ether solution (0.01–0.02 mol) was added with shaking for 1 hr. The solution was stirred overnight, boiled with charcoal, filtered, and evaporated in vacuo. The residue was chromatographed on neutral alumina (grade III) with benzene–methylene chloride (1:1) to give 180 mg of **13b** (21%), 30 mg of 1,3-dimethyluracil (5%), 370 mg of **14b** (41%), and 90 mg of several O-methylated 5-pyridyluracils (10%). Compounds **13b** and **14b** could be sublimed or recrystallized from benzene–hexane (1:1). Compound **14b:** mp 200–201°; ir (Nujol) 1705 and 1660 cm^{-1} (amide C=O); uv λ_{max} (95% ethanol) 243 nm (ϵ, 4600), 286 (6400); mass spectrum *m/e* (rel intensity) 217 (100), 202 (3), 189 (2), 159 (95), 132 (18), 119 (35), 103 (13). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.15; N, 19.34. Found: C, 60.94; H, 5.22; N, 19.29. Compound **13b:** mp 119–121°; ir (Nujol) 1695 and 1650 cm^{-1} (amide (C=O); uv λ_{max} (95% ethanol) 244 nm (ϵ 10800), 301 (11800); mass spectrum *m/e* (rel intensity) 217 (100), 202 (7), 189 (18), 132 (64), 131 (19), 117 (10). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.15; N, 19.34. Found: C, 60.95; H, 5.16; N, 19.25.

Reduction of the 1,3-Dimethyl-5-pyridyluracils 13b and 14b. In a typical experiment 150 mg (0.7 mmol) of sublimed **14b** was dissolved in 70 ml of 95% ethanol. A catalytic amount of palladium on charcoal was added and the reaction mixture was heated at 50°C under a H_2 pressure of 50 psi for 3 hr in a Paar apparatus. The reaction mixture was allowed to come to room temperature and the excess H_2 removed with a H_2O aspirator. The catalyst was removed by filtration and washed with two 10-ml portions of 95% ethanol and the ethanol was evaporated in vacuo to give an oil which was chromatographed on neutral alumina (grade III) with 1:1 acetonitrile–benzene to give 110 mg (75%) of **11b.** Compounds

11a and **11b** were oils that crystallized on long standing. **11b:** ir (Nujol) 1705, 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) τ 1.48 (d, 2 H), 2.47 (d, 1 H), 2.74 (q, 1 H), 6.06 (q, 1 H), 6.44 (m, 2 H), 6.88 (s, 3 H), 6.95 (s, 3 H); mass spectrum M^+ 219. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98. Found: C, 60.55; H, 6.08. **11a:** ir (Nujol) 1705, 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) τ 1.47 (d, d, 1 H), 2.36 (1, d, 1 H), 2.78 (m, 2 H), 6.03 (m, 2 H), 6.35 (q, 1 H), 6.80 (s, 3 H), 7.00 (s, 3 H); mass spectrum M^+ 219. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.19; H, 6.08; N, 19.06.

Reaction of Diazouracil 3 with Methyl Isonicotinate. To 17.40 g (0.12 mol) of methyl isonicotinate was added 1.40 g (8.0 mmol) of diazouracil **3**. The stirred reaction mixture was heated at 130° for 2 hr, allowed to come to room temperature, and added to 50 ml of hot H_2O. This suspension was continuously extracted with $CHCl_3$ for 48 hr. The H_2O suspension was evaporated in vacuo and the resulting residue was treated with excess CH_2N_2 in benzene. The resulting solution was treated with charcoal, evaporated in vacuo, and chromatographed on neutral alumina (grade III) with benzene–acetonitrile (9:1) to give 180 mg of **18b** (8%), 90 mg of **17b** (4%), 50 mg of **8** (5%), and mono-O-methylated products (3%). Compound **18b:** mp 233–234°; ir (Nujol) 1730, 1700, 1655 cm^{-1} (C=O); mass spectrum M^+ 275. Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.72; H, 4.76; N, 14.98.

Reaction of Diazouracil 3 with 4-Methoxypyridine. To 10 ml (0.10 mol) of 4-methoxypyridine was added 1.50 g (9.0 mmol) of diazouracil **3**. The stirred solution was heated at 130–135° for 3 hr. The crude reaction mixture was allowed to cool and added to 35 ml of hot H_2O. This brown slurry was continuously extracted with $CHCl_3$ for 48 hr. The H_2O suspension was evaporated in vacuo and the resulting solid dried in vacuo at 90°C for 1 hr. This residue showed molecular ions at *m/e* 222, 219, and 112. The residue was transferred with a small amount of CH_3OH and methylated with excess CH_2N_2–benzene. After shaking for 1 hr and standing overnight, the reaction mixture was treated with charcoal and chromatographed on neutral alumina (grade III) with benzene–acetonitrile progressing to ethanol to give 170 mg of **8** (13%), 290 mg of **19b** (13%), 140 mg of **20** (7%), 25 mg of **21b** (2%), and mono-O-methylated products (5%). In addition, some *N*-methyl-4-pyridone was also obtained. Compounds **20** and **21b** could be sublimed but **19b** partially (40–50%) rearranged to **20** on sublimation. Compound **19b:** mp 175° dec; ir (Nujol) 1695, 1655 cm^{-1} (C=O); mass spectrum M^+ 247. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.02; H, 5.42; N, 17.15. Compound **20:** mp 257–260°; ir (Nujol) 1685, 1645, 1555 cm^{-1} (C=O); mass spectrum M^+ 247. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.18; H, 5.35; N, 16.91. Compound **21b:** mp 254–256°; ir (Nujol) 1695, 1650 cm^{-1} (C=O); mass spectrum M^+ 278. Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.75; H, 5.08; N, 20.18.

Acknowledgment. The authors wish to thank Professor R. A. Abramovitch for interesting discussions.

Registry No.—**1**, 2435-76-9; **2**, 38099-09-1; **3**, 35124-90-4; **11a**, 56817-24-4; **11b**, 56817-25-5; **13a**, 56817-26-6; **13b**, 56817-27-7; **14a**, 56817-28-8; **14b**, 56817-29-9; **17b**, 56817-30-2; **18b**, 56817-31-3; **19b**, 56817-32-4; **20**, 56817-33-5; **21b**, 7033-42-3; pyridine, 110-86-1; methanol, 67-56-1; methyl isonicotinate, 2459-09-8; 4-methoxypyridine, 620-08-6.

References and Notes

(1) T. C. Thurber and L. B. Townsend, *J. Heterocycl. Chem.*, **9**, 629 (1972).
(2) T. C. Thurber and L. B. Townsend, *J. Am. Chem. Soc.*, **95**, 3081 (1973).
(3) T. C. Thurber, R. J. Pigmire, and L. B. Townsend, *J. Heterocycl. Chem.*, **11**, 645 (1974).
(4) S. H. Chang, I. Kim, and B.-S. Hahn, *Daehan Hwahak Hwoejee*, **9**, 75 (1965); *Chem. Abstr.*, **64**, 17588*g* (1965).
(5) F. G. Fischer and E. Fahr, *Justus Liebigs Ann. Chem.*, **651**, 65 (1962).
(6) Some leading references dealing with free-radical and carbene reactions in pyridines are: (a) R. A. Abramovitch, *Intra-Sci. Chem. Rep.*, **3**, 211 (1969); (b) R. A. Abramovitch and J. G. Saha, *Tetrahedron*, **21**, 3297 (1965); (c) R. A. Abramovitch and O. A. Koleoso, *J. Chem. Soc. B*, 1292 (1968); (d) *ibid.*, 779 (1969); (e) R. A. Abramovitch and J. G. Saha, *Adv. Heterocycl. Chem.*, **6**, 229–333 (1966).
(7) Unreported results from the senior authors laboratory.
(8) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Vol. 5, Pergamon Press, Elmsford, N.Y., 1969, p 307.

Carbon-13 Fourier Transform Nuclear Magnetic Resonance Spectroscopy of Indolo[2,3-*a*]quinolizidines. Specific Deuteration and Relaxation Methods in Structure Assignments[1]

Gordon W. Gribble,*[2] Randall B. Nelson,[3] Jerry L. Johnson,[4] and George C. Levy[5]

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, General Electric Corporate Research and Development, Schenectady, New York 12301, and Department of Chemistry, Florida State University, Tallahassee, Florida 32306.

Received April 9, 1975

The carbon-13 chemical shifts of the indole alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**), confirmed by selective deuteration, and the observed chemical shift differences between trans and cis C/D quinolizidine ring fusion in the 2-*tert*-butyl derivatives (**2** and **3**) are discussed in terms of steric compression and electronic effects. A two-bond deuterium-induced ^{13}C relaxation effect on the signal of nonprotonated carbons is observed and used for chemical shift assignments. The spin-lattice relaxation (T_1) times of **1** are an independent means of assigning chemical shifts, especially for nonprotonated carbons, and the results show that all of the carbons in **1** are relaxed primarily by the dipolar mechanism.

The past five years have seen enormous advances in the application of carbon-13 NMR spectroscopy to the structure elucidation and analysis of organic molecules.[6] Included in this array of compounds are plant indole alkaloids, which have recently been examined[7] by ^{13}C NMR, using the signal assignment techniques[6] of selective and off-resonance decoupling, lanthanide chelation, spectral comparison, and chemical shift considerations.

We wish to report a ^{13}C NMR study of the indole alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine[8] (**1**) (*Dracontomelum mangiferum*) using the techniques of carbon deuteration[9] and spin-lattice relaxation times[7b,10] to assign chemical shifts and to study relaxation pathways, and to report a study of the effect of ring conformation on the ^{13}C chemical shifts in the 2-*tert*-butyl derivatives **2** and **3**,[11] which have trans and cis C/D ring fusions, respectively.

The synthetic accessibility[8b] of **1** and its deuterated[8b,12] and alkyl[11] derivatives makes this alkaloid ideal for a ^{13}C NMR study as a simple model for the general class of *Corynanthe-Yohimbe* indole alkaloids.