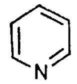
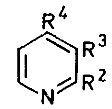
Tritium Nuclear Magnetic Resonance Spectroscopy. Part 10.[1] Distribution of Tritium in Some Labelled Nitrogen Heterocyclic Compounds

By **John A. Elvidge,* John R. Jones,*** and **Ramachandra B. Mane**, Chemistry Department, University of Surrey, Guildford GU2 5XH
Jasim M. A. Al-Rawi, Chemistry Department, University of Mosul, Mosul, Iraq

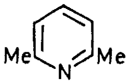
Pyridine, methylpyridines, quinoline, isoquinoline, phenanthridine, and nicotine have been labelled with tritium, using pre-reduced platinum dioxide and tritiated water. The regiospecificity and extent of labelling have been determined directly by ^{3}H n.m.r. In instances of non-uniform labelling, the predominant effect seems to have a steric origin. The hydrogen chemical shifts for phenanthridine are reported for the first time.

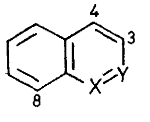
THE convenience and power of ^{3}H n.m.r. spectroscopy for investigating the distribution of tritium in tritiated compounds have already been indicated.[1-8] The technique seemed likely to prove especially helpful in detailed studies of catalysis, particularly for delineating the capabilities of those catalysts employed for hydrogen addition and for hydrogen exchange. A wide range of catalysts for these processes is available,[9] of both homogeneous and heterogeneous types. As a means of investigating the relative efficiencies of different catalysts, their orientation capabilities and selectivity, the effects of steric hindrance, and of poisoning, ^{3}H n.m.r. spectroscopy should be extremely effective. Detailed reaction mechanisms may well emerge from the new information that ^{3}H n.m.r. studies can provide, and we intend to investigate the possibilities.


(1)

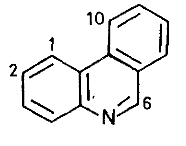

(2)

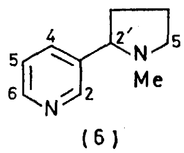
a; $R^2 = Me$, $R^3 = R^4 = H$
b; $R^3 = Me$, $R^2 = R^4 = H$
c; $R^4 = Me$, $R^2 = R^3 = H$


(3)


(4)

a; X = N, Y = CH
b; X = CH, Y = N


(5)


(6)

In this paper, we confine attention to some nitrogen heterocyclic compounds, pyridine (1), methylpyridines (2) and (3), quinoline and isoquinoline (4), phenanthridine (5), and nicotine (6), using divided platinum as catalyst (from the dioxide and borohydride) and with tritiated water as the source of hydrogen isotope. This catalyst has been shown to be one of the most active of transition metal catalysts.[10] Previous work with the platinum catalyst has mostly involved deuteriation studies, with mass spectrometry and ^{1}H n.m.r. spectroscopy being used to determine the labelling pattern. Investigations on tritiation have employed radio–g.l.c.[11] but this cannot provide direct information on the distribution of the label within particular molecular species. ^{3}H N.m.r. spectroscopy on the other hand is capable of providing complete analyses.[2-7]

EXPERIMENTAL

The catalyst was prepared by reduction [12] with sodium borohydride of platinum dioxide (Johnson Matthey Ltd.). To the heterocyclic compound (100 mg; purified) in a glass tube (100 × 5 mm diam.), freshly prepared catalyst (65 mg) was added, and the tube was closed with a serum cap, and evacuated through a syringe needle.[13] Tritiated water (10 μl; 50 Ci ml^{-1}) was added by syringe, and the (still evacuated) tube was sealed and heated at 125 °C for 65—80 h (125 h for nicotine). After being cooled, the tube was opened, the contents were extracted with ether (pentane for pyridine), and the solution was dried (Na_2SO_4), filtered, and evaporated. A portion of the tritiated compound (*ca.* 50 mg) was transferred to a 3 mm n.m.r. tube (Wilmad), along with solvent (see Table). A trace of tetramethylsilane was added and the tube was sealed under vacuum [13] and mounted in Teflon rings within a standard 5 mm n.m.r. tube. Deuterium oxide was placed in the annular space to provide for field-frequency locking. The internally referenced ^{3}H n.m.r. spectra were recorded at 96 MHz with ^{1}H noise decoupling, as previously described,[5,6] employing a Bruker WH90 pulse spectrometer.

RESULTS AND DISCUSSION

The lengthy times for the exchange reactions were chosen (after preliminary experimentation) to ensure full equilibration. The labelling results were closely reproducible (within ±10%). The integrity of the products was checked by ^{1}H n.m.r., the identity of the spectra with those of the starting materials confirming the absence of unexpected reactions. It should perhaps be mentioned that the tracer levels of incorporated tritium had no observable effect on the ^{1}H n.m.r. spectra [8] yet the sensitivity is such that the ^{3}H n.m.r. spectra are readily and rapidly acquired. The ^{1}H decoupled ^{3}H

Position and extent of tritium labelling in nitrogen heterocycles from ^3H n.m.r. data

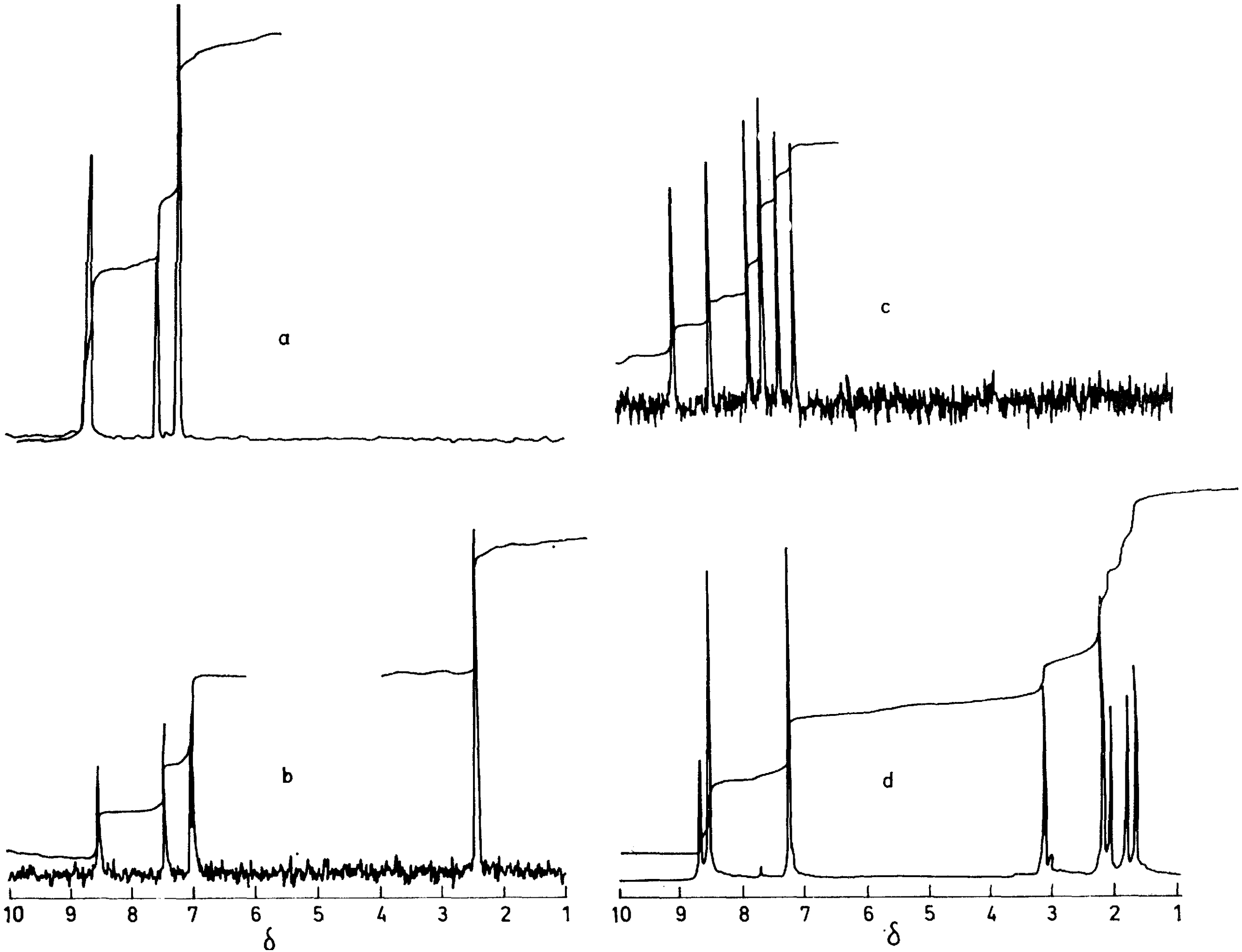
<table>
<tr><th>Compound</th><th>δ</th><th>Assignment</th><th>Signal intensity (%)</th><th>Relative incorporation per site</th></tr>
<tr><td>(1)</td><td>8.68 [a]</td><td>2,6</td><td>43</td><td>21.5</td></tr>
<tr><td></td><td>7.27</td><td>3,5</td><td>40</td><td>20</td></tr>
<tr><td></td><td>7.66</td><td>4</td><td>17</td><td>17</td></tr>
<tr><td>(2a)</td><td>2.45 [a]</td><td>2-Me</td><td>47</td><td>16</td></tr>
<tr><td></td><td>7.07</td><td>3</td><td>13</td><td>13</td></tr>
<tr><td></td><td>7.47</td><td>4</td><td>13</td><td>13</td></tr>
<tr><td></td><td>7.02</td><td>5</td><td>15</td><td>15</td></tr>
<tr><td></td><td>8.55</td><td>6</td><td>12</td><td>12</td></tr>
<tr><td>(2b)</td><td>2.27 [b]</td><td>3-Me</td><td>10</td><td>3.3</td></tr>
<tr><td></td><td>8.37</td><td>2</td><td>30</td><td>30</td></tr>
<tr><td></td><td>7.40</td><td>4</td><td>17</td><td>17</td></tr>
<tr><td></td><td>7.10</td><td>5</td><td>19</td><td>19</td></tr>
<tr><td></td><td>8.35</td><td>6</td><td>24</td><td>24</td></tr>
<tr><td>(2c)</td><td>2.29 [b]</td><td>4-Me</td><td>21</td><td>7</td></tr>
<tr><td></td><td>8.38</td><td>2,6</td><td>40</td><td>20</td></tr>
<tr><td></td><td>7.03</td><td>3,5</td><td>39</td><td>19.5</td></tr>
<tr><td>(3)</td><td>2.39 [b]</td><td>$2,6\text{-}Me_2$</td><td>76</td><td>12.7</td></tr>
<tr><td></td><td>6.82</td><td>3,5</td><td>7</td><td>3.5</td></tr>
<tr><td></td><td>7.33</td><td>4</td><td>17</td><td>17</td></tr>
<tr><td>(4a)</td><td>9.07 [a]</td><td>2</td><td colspan="2">13</td></tr>
<tr><td></td><td>7.14</td><td>3</td><td colspan="2">13</td></tr>
<tr><td></td><td>7.86</td><td>4</td><td colspan="2">16</td></tr>
<tr><td></td><td>7.62</td><td>5</td><td colspan="2">13</td></tr>
<tr><td></td><td>7.39</td><td>6</td><td colspan="2">14</td></tr>
<tr><td></td><td>7.64</td><td>7</td><td colspan="2">19</td></tr>
<tr><td></td><td>8.49</td><td>8</td><td colspan="2">12</td></tr>
<tr><td>(4b)</td><td>9.52 [a]</td><td>1</td><td colspan="2">14</td></tr>
<tr><td></td><td>8.84</td><td>3</td><td colspan="2">14</td></tr>
<tr><td></td><td>7.54</td><td>4</td><td colspan="2">12</td></tr>
<tr><td></td><td>7.62</td><td>5</td><td colspan="2">10</td></tr>
<tr><td></td><td>7.50</td><td>6</td><td colspan="2">18</td></tr>
<tr><td></td><td>7.41</td><td>7</td><td colspan="2">17</td></tr>
<tr><td></td><td>7.78</td><td>8</td><td colspan="2">15</td></tr>
<tr><td>(5)</td><td>8.43 [c]</td><td>1,10</td><td colspan="2">2</td></tr>
<tr><td></td><td>7.67</td><td>2</td><td colspan="2">14</td></tr>
<tr><td></td><td>7.56</td><td>3,8</td><td colspan="2">34</td></tr>
<tr><td></td><td>8.17</td><td>4</td><td colspan="2">11</td></tr>
<tr><td></td><td>9.17</td><td>6</td><td colspan="2">10</td></tr>
<tr><td></td><td>7.90</td><td>7</td><td colspan="2">13</td></tr>
<tr><td></td><td>7.70</td><td>9</td><td colspan="2">16</td></tr>
<tr><td>(6)</td><td>8.68 [a]</td><td>2</td><td colspan="2">4.9</td></tr>
<tr><td></td><td>7.72</td><td>4</td><td colspan="2">1</td></tr>
<tr><td></td><td>7.25</td><td>5</td><td colspan="2">18.3</td></tr>
<tr><td></td><td>8.54</td><td>6</td><td colspan="2">19.3</td></tr>
<tr><td></td><td>3.02</td><td>2′</td><td colspan="2">1</td></tr>
<tr><td></td><td>1.65</td><td>3′a [d]</td><td colspan="2">11.9</td></tr>
<tr><td></td><td>2.19</td><td>3′b</td><td colspan="2">15.9</td></tr>
<tr><td></td><td>1.81</td><td>4′a</td><td colspan="2">10.9</td></tr>
<tr><td></td><td>2.08</td><td>4′b</td><td colspan="2">6.9</td></tr>
<tr><td></td><td>3.12</td><td>5′b</td><td colspan="2">9.9</td></tr>
</table>

[a] Neat liquid. [b] 10% in CCl_4. [c] 18% in $CDCl_3$. [d] Symbols a and b refer to high and low field chemical shifts of hydrogen nuclei at the stated positions: 5′a is pseudoaxial, 4′a is pseudoequatorial, 3′ positions unassigned (see ref. 21).

spectra of the products (see Figure) gave, of course, single lines from each labelled position; these signals provided directly the required information on regiospecificity and extent of the labelling. The respective ^3H chemical shifts were assigned by reference to the analysed ^1H n.m.r. spectra (measured under comparable physical conditions) of pyridine,[14] the picolines and 2,6-lutidine,[15] quinoline,[16] and isoquinoline,[17] and the part-analysed ^1H spectrum of nicotine.[18] Recently the pyridine hydrogen chemical shifts were similarly derived direct from the ^1H decoupled ^2H n.m.r. spectrum,[19] and analogously for quinoline.[20] Further assignments for nicotine, apart from differentiation of the resonances from the 3′-positions, have been reported from ^1H decoupled ^2H spectra of some specifically deuteriated derivatives.[21] In the case of phenanthridine, for which the ^1H n.m.r. spectrum has not yet been fully analysed,[22] we have assigned the ^3H chemical shifts by comparison with those for quinoline and isoquinoline and the ^1H data for phenanthrene.[23]

The ^3H n.m.r. chemical shifts of the tritiated products, the assignments, and information on tritium incorporation are listed in the Table. The incorporation data have been derived directly from the ^1H noise-decoupled ^3N n.m.r. signal intensities. Possible errors arising from differential nuclear Overhauser effects (n.O.e.) are generally so small as not to warrant the extra time required for taking spectra with full n.O.e. suppression.[24]

The platinum-tritiated water reagent labels pyridine (1) and 2-picoline (2a) particularly uniformly, as the last column of the Table indicates. With 3-picoline (2b) and 4-picoline (2c), preference for exchange at the ring positions rather than the methyl groups is apparent, whilst with 2,6-lutidine (3) exchange at the ring 3- and 5-positions is strongly inhibited. That neither simple electronic considerations nor minor steric factors can reliably be invoked to account for or predict the exchange results is further illustrated by the fairly uniform labelling achieved in quinoline (4a) and isoquinoline (4b). However, where steric hindrance is marked, as at the 1- and 10-positions in phenanthridine (5), exchange is largely inhibited. This finding agrees with the results for polycyclic aromatic hydrocarbons obtained under slightly different exchange conditions.[6] Finally, employing nicotine (6) as substrate, it was observed that the platinum-tritiated water reagent ultimately (125 h) effects exchange at all the ring positions in both rings except for the pseudo-axial 5′a-position *cis*-disposed to the (pseudo-equatorial) *N*-methyl group in the pyrrolidine ring. With a shorter exchange time (65 h) both 5′-positions remain unlabelled and the degree of exchange at the other pyrrolidine ring positions is low relative to that in the pyridine ring. These observations agree with other of our findings which indicate the operation of a ' progressive ' mechanism in the exchange labelling of alkyl aromatic compounds with platinum catalyst. It is recognised that adsorption of the aryl ring onto the catalyst leads to arylmetal species which undergo hydrogen migration and exchange.[10,25] It appears to us that the metal–carbon bonding can undergo progressive 1,2-migration (with concomitant hydrogen migration, and so exchange) so that even long alkyl chains attached to aryl rings become labelled right to the end, although the degree of labelling falls off with distance from the ring. A heteroatom bearing no hydrogen, if present in such a side chain, thus blocks the exchange beyond that position completely. For this reason we considered that the *N*-methyl group of the pyrrolidine moiety of nicotine (δ 2.18) [18] would not be labelled and that the observed ^3H resonance at δ 2.19 could then be assigned only to the 3′b-position. Confirmation of the absence of label in the *N*-methyl group came from comparisons of the spectrum with the ^1H undecoupled



^3H N.m.r. spectra (with ^1H decoupling) of [G-^3H] compounds: a, pyridine; b, 2-picoline; c, quinoline; d, nicotine

^3H n.m.r. spectrum and with the ^1H n.m.r. spectrum of the same sample.

We gratefully acknowledge support from the S.R.C. and The Radiochemical Centre Ltd.

[8/1043 *Received, 5th June,* 1978]

REFERENCES

[1] Part 9, J. A. Elvidge, J. R. Jones, R. B. Mane, V. M. A. Chambers, E. A. Evans, and D. C. Warrell, *J. Labelled Compounds*, 1978, **14**, 141.

[2] J. A. Elvidge, J. R. Jones, M. A. Long, and R. B. Mane, *Tetrahedron Letters*, 1977, 4349.

[3] J. A. Elvidge, D. K. Jaiswal, J. R. Jones, and R. Thomas, *J.C.S. Perkin 1*, 1977, 1080.

[4] J. P. Bloxsidge, J. A. Elvidge, J. R. Jones, R. B. Mane, V. M. A. Chambers, E. A. Evans, and D. Greenslade, *J. Chem. Res.* (*S*), 1977, 42.

[5] J. M. A. Al-Rawi, J. P. Bloxsidge, J. A. Elvidge, J. R. Jones, V. E. M. Chambers, V. M. A. Chambers, and E. A. Evans, *Steroids*, 1976, **28**, 359.

[6] J. M. A. Al-Rawi, J. P. Bloxsidge, J. A. Elvidge, J. R. Jones, V. M. A. Chambers, and E. A. Evans, *J. Labelled Compounds*, 1976, **12**, 293.

[7] J. M. A. Al-Rawi, J. A. Elvidge, J. R. Jones, V. M. A. Chambers, and E. A. Evans, *J. Labelled Compounds*, 1976, **12**, 265.

[8] J. P. Bloxsidge, J. A. Elvidge, J. R. Jones, and E. A. Evans, *Org. Magnetic Resonance*, 1971, **3**, 127.

[9] E. A. Evans, 'Tritium and its Compounds,' Butterworths, London, 1974, 2nd edn., ch. 4.

[10] G. E. Calf and J. L. Garnett, *Adv. Heterocyclic Chem.*, 1973, **15**, 137.

[11] J. L. Garnett, *Nucleonics*, 1962, **20**, 86.

[12] G. E. Calf and J. L. Garnett, *J. Phys. Chem.*, 1964, **68**, 3887.

[13] J. M. A. Al-Rawi and J. P. Bloxsidge, *Org. Magnetic Resonance*, 1977, **10**, 261.

[14] G. Fraenkel, D. G. Adams, and R. R. Dean, *J. Phys. Chem.*, 1968, **72**, 944; T. Tokuhiro, N. K. Wilson, and G. Fraenkel, *J. Amer. Chem. Soc.*, 1968, **90**, 3622.

[15] J. N. Murrell and V. M. S. Gil, *Trans. Faraday Soc.*, 1965, **61**, 402; W. Brügel, *Z. Elektrochem.*, 1962, **66**, 159.

[16] P. J. Black and M. L. Heffernan, *Austral. J. Chem.*, 1964, **17**, 558.

[17] P. J. Black and M. L. Heffernan, *Austral. J. Chem.*, 1966, **19**, 1287.

[18] N. S. Bhacca, E. F. Johnson, and J. N. Shoolery, 'NMR Spectra Catalog,' Varian Associates, Palo Alto, 1962, vol. 1, no. 269.

[19] T. P. Pitner, J. F. Whidby, and W. B. Edwards, *Analyt. Chem.*, 1977, **49**, 674.

[20] H. H. Mantsch, H. Saito, and I. C. P. Smith, *Progr. N.M.R. Spectroscopy*, 1977, **11**, 211.

[21] T. P. Pitner, W. B. Edwards, R. L. Bassfield, and J. F. Whidby, *J. Amer. Chem. Soc.*, 1978, **100**, 246.

[22] Sadtler Standard Spectra, No. 19497M.

[23] R. C. Fahey and G. C. Graham, *J. Phys. Chem.*, 1965, **69**, 4417.

[24] J. P. Bloxsidge, J. A. Elvidge, J. R. Jones, R. B. Mane, and E. A. Evans, *J. Chem. Res.* (*S*), 1977, 258.

[25] E. Crawford and C. Kemball, *Trans. Faraday Soc.*, 1962, **58**, 2452; C. G. Macdonald and J. S. Shannon, *Austral. J. Chem.*, 1965, **18**, 1009.