Ring-opening Reactions of Halogenated *N*-Aryl-1,2,3,4-tetrahydroisoquinoline and 2,3,4,5-Tetrahydro-1*H*-2-benzazepine Derivatives

Alan L. Stanley and Stephen P. Stanforth*

Department of Chemical and Life Sciences,
University of Northumbria at Newcastle,
Newcastle upon Tyne, NE1 8ST, UK
Received October 25, 1994

Compounds **4a-4d**, **4f** and **10** were prepared and their ring-opening reactions with *N*-bromosuccinimide (NBS) investigated. Compounds **4a** and **4b** gave a mixture of products which did not contain any significant quantity of the corresponding aldehydes **5a** and **5b** whereas compounds **4c**, **4d** and **4f** gave exclusively the aldehydes **5c**, **5d** and **5f** respectively. Compound **10** similarly gave the aldehyde **11** when treated with NBS.

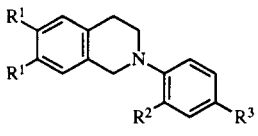
J. Heterocyclic Chem., **32**, 569 (1995).

We have recently described the preparation of nitroaldehydes **2a** and **2b** by treatment of the 1,2,3,4-tetrahydroisoquinoline derivatives **1a** and **1b** with NBS followed by basic work-up [1]. These two compounds existed exclusively as the aldehyde structures **2a** and **2b** and none of the corresponding hemi-aminals **3a** and **3b** could be detected. One factor which could contribute to the preference of the aldehyde structures is the potential for intra-molecular hydrogen bonding between the appositely located nitro-group and the >NH group: this has been confirmed by an X-ray crystallographic examination of compound **2a** [2]. In compounds possessing a 4-nitroaryl substituent where intra-molecular hydrogen bonding is precluded, either the hemi-aminal is favoured as in the case of compound **3c** [3], or the aldehyde is preferred as in the case of compound **3d** [1]. This contrast between hemi-aminal and aldehyde formation in these two cases could only be attributed to the steric effect of the methyl group since the inductive effect of this group would be expected to favour the hemi-aminal **3d** by comparison with compound **3c**. Electron-releasing groups in the tetrahydroisoquinoline ring can also effect the balance between aldehyde and hemi-aminal structures. Thus, electron delocalisation between the 6-methoxy substituent and the aldehyde group in compound **2e** favours this aldehyde structure [4] in contrast to the hemi-aminal **3c** structure noted above.

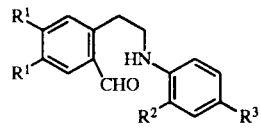
We next turned our attention to *N*-aryl compounds which did not contain a nitro-group and the fluorinated compounds **4** were chosen for study. These compounds, with the exception of compound **4e** were readily prepared in good yield by the reaction of 1,2,3,4-tetrahydroisoquinoline, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline or 2,3,4,5-tetrahydro-1*H*-2-benzazepine with either hexafluorobenzene or pentafluoropyridine as appropriate under basic conditions. Suprisingly, we were unable to obtain compound **4e** from 1,2,3,4-tetrahydroisoquinoline and hexafluorobenzene. In compounds **4c**, **4d** and **4f** which all possess an *N*-tetrafluoropyridyl group, their fluorine nmr spectra all exhibited two signals centred at -91.1 to -91.6 and -151.1 to -153.0 ppm relative to fluorotrichloromethane (AA'XX' system) which indicated that substitution had occurred at the 4-position of the pyridine ring.

When compound **4a** was treated with NBS examination by proton nmr spectroscopy of the crude reaction product after basic work-up showed a mixture of products and no aldehyde signal was apparent indicating the absence of compound **5a**. If the hemi-aminal **6a** had been formed in this reaction, there were clearly some additional products present as well. When this mixture of products was oxidised with chromium trioxide in acetic acid the lactam **7** was formed (91% from compound **4a**) which suggested the presence of the hemi-aminal **6a** and/or the diasterioisomeric ethers **8** in the reaction mixture. Ethers such as **8** could be formed from two hemi-aminals **6a** by loss of water and similar types of compounds have been reported [4]. Thus, an equilibrium mixture of compounds **6a** and **8** could well be the products obtained from treatment of compound **4a** with NBS and during the oxidation with chromium trioxide ethers **8** and water equilibrate with the hemi-aminal **6a** which is then oxidised to lactam **7**. Similarly, compound **4b** yielded a mixture of products when treated with NBS and again no aldehyde signal was apparent. In this reaction, the 6-methoxy substituent is unable to assist the formation of the aldehyde structure **5b**. When compounds **4c**, **4d** and **4f** were treated with NBS, the aldehydes **5c**, **5d** and **5f** respectively were formed. The *N*-tetrafluoro-4-pyridyl subsituent is now sufficiently electron-withdrawing to preclude hemi-aminal formation.

We next decided to investigate the ring-opening reaction of some related chlorinated compounds. When 1,2,3,4-tetrahydroisoquinoline was reacted with pentachloropyridine the proton nmr spectra of the crude reaction product displayed two methylene signals which were attributed to a mixture of two regioisomers **9** and **10**. Fractional recrystallisation of this mixture gave a single compound which was identified as the major regioisomer **10** because its carbon nmr spectrum showed fourteen sig-



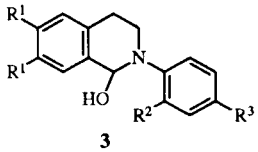
1



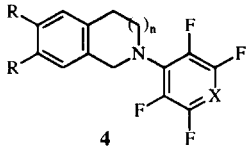
2

For compounds **1-3**

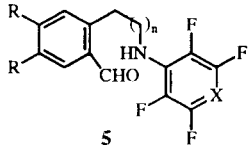
	R^1	R^2	R^3
a	H	NO_2	H
b	H	NO_2	Me
c	H	H	NO_2
d	H	Me	NO_2
e	OMe	H	NO_2



3



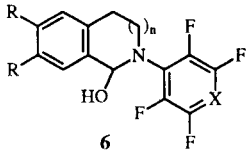
4



5

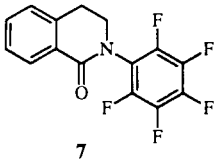
For compounds **4-6**

	n	R	X
a	1	H	CF
b	1	OMe	CF
c	1	H	N
d	1	OMe	N
e	2	H	CF
f	2	H	N

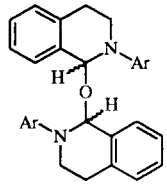


6

nals. When compound **10** was treated with NBS the aldehyde **11** (98% yield) was obtained and their was no evidence of the corresponding hemi-aminal.

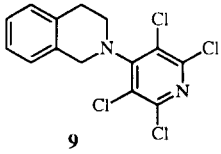


7

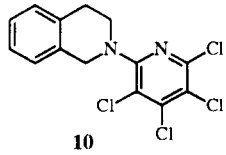


8

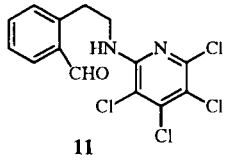
Ar = pentafluorophenyl



9



10



11

In conclusion, the pentafluorophenyl group is not sufficiently electron withdrawing to favour the aldehyde structures whereas the tetrafluoropyridyl or tetrachloropyridyl groups do favour the aldehyde structures.

EXPERIMENTAL

Proton and carbon nmr spectra were determined in deuteriochloroform solution at 90 MHz using tetramethylsilane as an internal standard. Infra-red spectra were recorded as potassium bromide discs.

Compounds **4**, **9** and **10**. General Method.

A mixture of 1,2,3,4-tetrahydroisoquinoline (THIQ) or 6,7-dimethoxy-THIQ hydrochloride or 2,3,4,5-tetrahydro-1*H*-2-benzazepine [5] potassium carbonate and the appropriate haloaryl compound were heated (100°) in dimethylsulfoxide (0.5-2 hours) with stirring. The mixture was poured into water and the product was extracted into dichloromethane. The organic layer was washed several times with water, dried (magnesium sulfate) and evaporated giving the product.

N-Pentafluorophenyl-1,2,3,4-tetrahydroisoquinoline **4a**.

THIQ (2.08 g), potassium carbonate (4.0 g) and hexafluorobenzene (2.90 g) gave compound **4a**, 3.51 g (75%) as cream needles, mp 89-91° (from ethanol); ir: ν 2850, 1515, 1495, 1141 and 986 cm^{-1}; ^{1}H-nmr: δ 7.20 (4H, m, ArH), 4.89 (2H, s, $>CH_2$), 3.50 (2H, t, J = 7 Hz, $-CH_2CH_2-$) and 3.00 (2H, t, J = 7 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{15}H_{10}F_5N$: C, 60.2; H, 3.4; N, 4.7. Found: C, 60.25; H, 3.3; N, 4.65.

N-Pentafluorophenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **4b**.

6,7-Dimethoxy-THIQ•HCl (2.00 g), potassium carbonate (3.30 g) and hexafluorobenzene (1.04 g) gave compound **4b**, 2.08 g (70%) as cream needles, mp 143-145° (from ethanol); ir: ν 3000, 1615, 1515, 1495, 1260, 1115, 970 and 810 cm^{-1}; ^{1}H-nmr: δ 6.55 (2H, d, J = 10 Hz, ArH), 4.30, (2H, s, $>CH_2$), 3.87 (3H, s, -OMe), 3.85 (3H, s, -OMe), 3.46 (2H, t, J = 6 Hz, $-CH_2CH_2-$) and 2.89 (2H, t, J = 6 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{17}H_{14}F_5NO_2$: C, 56.8; H, 3.9; N, 3.9. Found: C, 56.85; H, 4.00; N, 4.05.

N-(2',3',5',6'-Tetrafluoro-4'-pyridyl)-1,2,3,4-tetrahydroisoquinoline **4c**.

THIQ (2.00 g), potassium carbonate (4.20 g) and pentafluoropyridine (2.70 g) gave compound **4c**, 4.00 g (94%) as colorless plates, mp 97-98° (from ethanol); ir: ν 1640, 1525, 1460, 1135, 950 and 760 cm^{-1}; ^{1}H-nmr: δ 7.23 (4H, m, ArH), 4.72 (2H, s, $>CH_2$), 3.75 (2H, t, J = 7 Hz, $-CH_2CH_2-$) and 3.03 (2H, t, J = 7 Hz, $-CH_2CH_2-$) ppm.

Anal. Calcd. for $C_{14}H_{10}F_4N_2$: C, 59.6; H, 3.6; N, 9.9. Found: C, 59.55; H, 3.55; N, 10.05.

N-(2',3',5',6'-Tetrafluoro-4'-pyridyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **4d**.

6,7-Dimethoxy-THIQ•HCl (2.00 g), potassium carbonate (3.60 g) and pentafluoropyridine (1.34 g) gave compound **4d**, 2.80 g (91%) as colorless needles, mp 155-156° (from ethanol); ir: ν 3000, 1635, 1515, 1450, 1140 and 940 cm^{-1}; ^{1}H-nmr: δ 6.65 (1H, s, ArH), 6.50 (1H, s, ArH), 4.65 (2H, s, $>CH_2$), 3.95 (3H, s, -OMe), 3.92 (3H, s, -OMe), 3.73 (2H, t, J = 6 Hz,

-CH_2CH_2-) and 2.95 (2H, t, J = 6 Hz, -CH_2CH_2-) ppm.

Anal. Calcd. for $C_{16}H_{14}F_4N_2O_2$: C, 56.1; H, 4.1; N, 8.2. Found: C, 56.2; H, 4.1; N, 8.2.

N-(2',3',5',6'-Tetrafluoro-4'-pyridyl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine **4f**.

2,3,4,5-Tetrahydro-1*H*-2-benzazepine (0.30 g), potassium carbonate (0.60 g) and pentafluoropyridine (0.34 g) gave compound **4f**, 0.40 g (68%) as colorless needles, mp 100-102° (from ethanol); ir: ν 1625, 1515, 1480, 1130 and 955 cm^{-1}; ^{1}H-nmr: δ 7.18 (4H, s, ArH), 4.69 (2H, s, >CH_2), 3.82 (2H, t, J = 6 Hz, -$CH_2CH_2CH_2$-), 3.05 (2H, t, J = 6 Hz, -$CH_2CH_2CH_2$-) and 2.01 (2H, q, J = 6 Hz, -$CH_2CH_2CH_2$-) ppm.

Anal. Calcd. for $C_{15}H_{12}F_4N_2$: C, 60.8; H, 4.1; N, 9.5. Found: C, 60.95; H, 4.0; N, 9.4.

N-(2',3',4',5'-Tetrachloro-6'-pyridyl)-1,2,3,4-tetrahydroisoquinoline **10**.

THIQ (2.66 g), potassium carbonate (5.0 g) and pentachloropyridine (5.0 g) gave a mixture of compounds **9** and **10**, 5.38 g (77%). Fractional recrystallisation from ethanol gave compound **10** as colorless needles, mp 141°; ir: ν 3000, 1550, 1500, 1425, 1300, 1205, 1145, 1030, 930 and 805 cm^{-1}; ^{1}H-nmr: δ 7.20 (4H, s, ArH), 4.59 (2H, s, >CH_2), 3.71 (2H, t, J = 6 Hz, -CH_2CH_2-) and 3.09 (2H, t, J = 6 Hz, -CH_2CH_2-) ppm; ^{13}C-nmr 155.9, 144.9, 143.8, 134.3, 133.7, 128.9, 126.6 (two signals), 126.1, 120.7, 119.0, 50.8, 47.7 and 29.0 ppm.

Anal. Calcd. for $C_{14}H_{10}Cl_4N_2$: C, 48.3; H, 2.9; N, 8.05. Found: C, 48.1; H, 2.7; N, 8.05.

Reaction of *N*-Aryl-1,2,3,4-tetrahydroisoquinoline Derivatives with NBS.

A mixture of the appropriate aryl compound **4** or **10**, NBS and a few crystals of dibenzoyl peroxide were heated at reflux in dichloromethane until the reaction was complete (tlc). After cooling to room temperature, the mixture was washed with dilute sodium hydroxide solution and then with water, dried (magnesium sulfate) and evaporated giving the product. The products obtained from reaction of compound **4a** with NBS were oxidised with sodium dichromate giving compound **7** (see below).

N-Pentafluorophenyl-3,4-dihydroisoquinol-1-one **7**.

Compound **4a** (0.21 g) and NBS (0.14 g) gave a mixture of products (see text). To this mixture (0.20 g) in acetic acid (5 ml) was added a solution of sodium dichromate (0.60 g) in acetic acid (5 ml) dropwise. The mixture was heated at reflux (2 hours) allowed to cool to room temperature, poured into water and extracted with dichloromethane. The organic extracts were washed with water, dried (magnesium sulfate) and evaporated giving compound **7**, 0.20 g (91%) as a white powder, mp 100-102° (from aqueous ethanol); ir: ν 1730, 1675, 1650, 1505, 1470, 1415, 1230, 1215, 1175, 1000, 985 and 745 cm^{-1}; ^{1}H-nmr: δ 8.13 (1H, dd, J = 8 and 2 Hz, ArH), 7.95 (1H, d, J = 8 Hz, ArH), 7.40 (2H, m, ArH), 3.90 (2H, t, J = 6 Hz, -CH_2CH_2-) and 3.20 (2H, t, J = 6 Hz, -CH_2CH_2-) ppm.

Anal. Calcd. for $C_{15}H_8F_5NO$: C, 57.5; H, 2.6; N, 4.5. Found: C, 57.7; H, 2.9; N, 4.25.

N-(2',3',5',6'-Tetrafluoro-4'-pyridyl)-2-(aminoethyl)benzaldehyde **5c**.

Compound **4c** (1.00 g) and NBS (0.66 g) gave compound **5c**, 1.00 g (97%) as colorless plates, mp 155-156° (from acetone); ir: ν 3375, 1705, 1690, 1550, 1475 and 1150 cm^{-1}; ^{1}H-nmr: δ 10.10 (1H, s, -CHO), 7.80 (1H, dd, J = 11 and 3 Hz, ArH), 7.54 (2H, m, ArH), 7.31 (1H, dd, J = 11 and 3 Hz, ArH), 5.05 (1H, broad s, >NH), 3.80 (2H, t, J = 7 Hz, -CH_2CH_2-) and 3.38 (2H, t, J = 7 Hz, -CH_2CH_2-) ppm.

Anal. Calcd. for $C_{14}H_{10}F_4N_2O$: C, 56.4; H, 3.4; N, 9.4. Found: C, 56.2; H, 3.35; N, 9.60.

N-(2',3',5',6'-Tetrafluoro-4'-pyridyl)-4,5-dimethoxy-2-(aminoethyl)-benzaldehyde **5d**.

Compound **4d** (1.50 g) and NBS (0.86 g) gave compound **5d**, 1.44 g (90%) as cream needles, mp 144-145° (from ethanol); ir: ν 3400, 1675, 1640, 1560, 1485, 1265, 1158 and 1125 cm^{-1}; ^{1}H-nmr: δ 10.03 (1H, s, -CHO), 7.29 (1H, s, ArH), 6.73 (1H, s, ArH), 5.15 (1H, broad s, >NH), 3.96 (3H, s, -OMe), 3.95 (3H, s, -OMe), 3.80 (2H, t, J = 6 Hz, -CH_2CH_2-), and 3.33 (2H, t, J = 6 Hz, -CH_2CH_2-) ppm.

Anal. Calcd. for $C_{16}H_{14}F_4N_2O_3$: C, 53.6; H, 3.9; N, 7.8. Found: C, 53.4; H, 3.95; N, 7.65.

N-(2',3',5',6'-Tetrafluoro-4'-pyridyl)-2-(aminopropyl)benzaldehyde **5f**.

Compound **4f** (0.15 g) and NBS (0.10 g) gave compound **5f**, 0.12 g (76%) as colorless needles, mp 96-97° (from ethanol); ir: ν 3390, 2990, 2920, 1720, 1670, 1580, 1510, 1380, 1340, 1210, 1185 and 995 cm^{-1}; ^{1}H-nmr: δ 10.10 (1H, s, -CHO), 7.80 (1H, d, J = 8 Hz, ArH), 7.45 (2H, m, ArH), 7.26 (1H, d, J = 8 Hz, ArH), 5.20 (1H, broad s, >NH), 3.65 (2H, t, J = 8 Hz, -$CH_2CH_2CH_2$-), 3.10 (2H, t, J = 8 Hz, -$CH_2CH_2CH_2$-) and 2.00 (2H, q, J = 8 Hz, -$CH_2CH_2CH_2$-) ppm.

Anal. Calcd. for $C_{15}H_{12}F_4N_2O$: C, 57.7; H, 3.9; N, 9.0. Found: C, 57.45; H, 3.75; N, 8.9.

N-(2',3',4',5'-Tetrachloro-6'-pyridyl)-2-(aminoethyl)benzaldehyde **11**.

Compound **10** (0.36 g) and NBS (0.20 g) gave compound **11**, 0.36 g (98%) as colorless plates, mp 149-151° (from ethanol); ir: ν 3000, 1695, 1570 and 1485 cm^{-1}; ^{1}H-nmr: δ 10.25 (1H, s, -CHO), 7.85 (1H, dd, J = 9 and 2 Hz, ArH), 7.60-7.45 (3H, m, ArH), 5.58 (1H, broad s, >NH), 3.72 (2H, t, J = 6 Hz, -CH_2CH_2-) and 3.40 (2H, t, J = 6 Hz, -CH_2CH_2-) ppm.

Anal. Calcd. for $C_{14}H_{10}Cl_4N_2O$: C, 46.2; H, 2.8; N, 7.7. Found: C, 46.05; H, 2.55; N, 7.60.

Acknowledgements.

We wish to thank Rhone Poulenc for generous financial support and the SERC for a CASE award (to A. L. S). We also thank Dr. M. P. L. Caton of Rhone Poulenc for advice and encouragement.

REFERENCES AND NOTES

[1] K. A. Hedley and S. P. Stanforth, *Tetrahedron*, **48**, 743 (1992).

[2] W. Clegg, S. P. Stanforth, K. A. Hedley, E. S. Raper and J. R. Creighton, *Acta. Crystallogr.*, **C50**, 583 (1994).

[3] J. Streith and C. Fizet, *Tetrahedron Letters*, 3297 (1977).

[4] D. Beke, *Adv. Heterocyclic Chem.*, **1**, 167 (1963).

[5] A. E. Meyers and I. Hutchings, *Tetrahedron*, **49**, 1807 (1993).