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DIAZAINDENES (AZAINDOLES)—IV[1]

OXIDATION OF 1,5- AND 1,7-DIAZAINDENES AND A NOVEL ROUTE TO 3-SUBSTITUTED DIAZAINDENES

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Abstract—Treatment of certain 1,5- and 1,7-diazaindenes with a small molar excess of hydrogen peroxide in acetic acid causes opening of the pyrrole ring with loss of the 2-C atom to give aminopyridyl ketones or aminopyridine carboxylic acids. The former have been used as intermediates in the synthesis of 3-substituted diazaindenes by reaction with dimethylsulphonium methylide. Stable iodine complexes with 1,5-diazaindenes may be formed: 6-(4-aminopyrid-3-yl)-6-oxohexanoic acid gave 4-(1-methyl-1,5-diazainden-3-yl)butanoic acid.

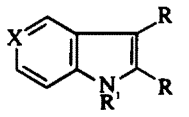
We have attempted to prepare the oxides, **1** and **5**, by oxidation of 1,5- (**2**) and 1,7-diazaindene (**6**) respectively, since these oxides would be useful intermediates in the synthesis of analogues of the recently discovered pyrrolopyrimidine nucleoside antibiotics. Our initial attempts to obtain the N-oxides were unsuccessful, but some of the results obtained have led to the development of a novel and potentially useful route to 3-substituted diazaindenes.

Recently α-carboline has been converted into α-carboline N-oxide by treatment with hydrogen peroxide–acetic acid mixture.[3] When **2** and **6** were treated separately with a similar oxidising medium (containing 1·5 molar equivalents of hydrogen peroxide) only 4-aminonicotinic acid and 2-aminonicotinic acid, respectively were obtained. The 2-C atom of the diazaindene is lost in the oxidation process. Protection of the pyrrole N atom, by formation of 1-acetyl-1,5-diazaindene (**3**) before attempted N-oxidation, did not alter the course of the reaction: 1-acetyl-1,5-diazaindene yielded 4-aminonicotinic acid. Hydrolysis of the N-acetyl group to produce an equilibrium concentration of **2** must occur rapidly in the acetic acid containing a small quantity of water, and this idea agrees with the finding[4] that N-acetylcarbazole in acetic acid containing a few drops of dilute hydrochloric acid quickly undergoes hydrolysis to carbazole.

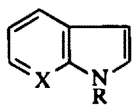
The results obtained with the parent diazaindenes are in contrast to those reported by Crooks[5] who, on treatment of 2,3-dimethyl-1,5-diazaindene (**4**) with an acetic acid–hydrogen peroxide mixture obtained 3-acetyl-4-acetamidopyridine 1-oxide, **8**; a product formed by N-oxidation and, presumably, oxidation of the pyrrole moiety without loss of the 2-C atom. It was, therefore, of interest to try the oxidation of 2,3-dimethyl-1,5-diazaindene under the conditions used in our experiments, and this yielded 3-acetyl-4-aminopyridine, **9**.

Application of the reaction to both 6, 7, 8, 9 - tetrahydro - γ - carboline, **14**, and its 1-acetyl derivative, **15**, gave the same product, which was not likely to be an N-oxide since its mass spectrum did not show an M-16 peak. Elemental analysis and MS data indicated a molecular formula, $C_{11}H_{14}N_2O_3$. IR spectroscopy showed the presence of two CO groups, an NH_2 and an OH group. NMR spectroscopy showed the presence of a saturated alkyl chain containing 8 H atoms and the compound was assigned the structure 6-(4-aminopyrid-3-yl)-6-oxohexanoic acid, **10**. A corresponding product, 6 - (2 - anilo) - 6 - oxohexanoic acid, **11**, has previously been obtained[6] by the oxidation of 1, 2, 3, 4 - tetrahydrocarbazole, **16**, in the presence of oxygen and a platinum catalyst.

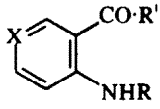
It seems likely that, in all the cases that we have investigated, cleavage of the 2,3-bond of the diazaindene occurs to give a dicarbonyl compound, *e.g.* **12**, **13** or **18**, in a similar manner to that suggested[7] for tetrahydrocarbazole oxidation. These intermediates then readily undergo hydrolysis of the amide to give the products. Since only 1·5 molar equivalents of hydrogen peroxide were used, it was possible that the ring cleavage reaction was much more rapid than N-oxidation and that the peroxide and peracid were removed before significant N-oxidation could occur. The reaction conditions used in this work were similar to those used to convert α-carboline to its N-oxide.[3] In order to provide some information about the ease of N-oxidation of the 1,5-diazaindene system, this reaction was applied to α-carboline, an aromatic ring system which would be unlikely to undergo ring cleavage under these mild conditions; only the



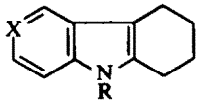
1: R = R' = H, X = $\overset{+}{N}$—$\overset{-}{O}$
2: R = R' = H, X = N
3: R = H, R' = $COCH_3$, X = N
4: R = R' = CH_3, X = N



5: R = H, X = $\overset{+}{N}$—$\overset{-}{O}$
6: R = H, X = N
7: R = $COCH_3$, X = N



8: R = $COCH_3$, R' = CH_3, X = $\overset{+}{N}$—$\overset{-}{O}$
9: R = H, R' = CH_3, X = N
10: R = H, R' = $(CH_2)_4 \cdot CO_2H$, X = N
11: R = H, R' = $(CH_2)_4 \cdot CO_2H$, X = CH
12: R = $COCH_3$, R' = OH, X = N
13: R = $COCH_3$, R' = CH_3, X = N



14: R = H, X = N
15: R = $COCH_3$, X = N
16: R = H, X = CH
17: R = CH_3, X = N

starting material (95%) was isolated. Thus, in no case was N-oxidation of a 1,5-diazaindene system achieved using the hydrogen peroxide–acetic acid mixture. The difference in reactivity of α- and γ-carboline may be associated with the greater basicity of the 1,5-diazaindene compared to the 1,7-diazaindene system.[8]

Recently, the synthesis of certain indoles has been reported[9] using the reaction of *o*-aminophenyl ketones and aldehydes with dimethylsulphonium methylide. An analogous system exists in the diazaindene oxidation products **9** and **10**, and it seemed possible that the ylide could be used to obtain other diazaindenes from them, provided that the 4-amino groups had sufficient nucleophilic power to bring about the cyclisation step. Treatment of 3 - acetyl - 4 - aminopyridine with the ylide readily gave the cyclised product, 3 - methyl - 1, 5 - diazaindene, **19**. No N-methylated product was obtained, in contrast to the result with *o*-aminoacetophenone.[9]

On treatment of the potassium salt of **10** with the ylide, a product was obtained only after acidification of the reaction mixture. The product was black and attempts to remove the colour were unsuccessful. Elemental analysis and mass spectroscopy indicated a molecular formula $C_{13}H_6N_2O_2 + I_2$; the iodine presumably being present as part of a charge-transfer complex with the pyridine ring and this being responsible for the colour of the compound. The H^1 NMR spectrum indicated that a 3-substituted-1,5-diazaindene had been formed, the eight protons of the alkyl chain and a low field exchangeable proton were apparent. An unexpected feature was the presence of a singlet at δ 3·98 corresponding to a Me group. The NMR spectra of this compound and a number of diazaindene derivatives are given in Table 1. The 4-, 6-, and 7-protons are shifted down field from their positions in the spectrum of 1,5-diazaindene and have similar chemical shifts to the corresponding protons in diazaindene methiodides. However, the Me group protons attached to a quaternary N atom in 1,5-diazaindene and tetrahydro-γ-carboline methiodides appear at δ 4·43 and 4·60, which are clearly different from the group at δ 3·98, but this is similar to a peak at δ 3·93 due to the 5-Me group in the methiodide of **17**.

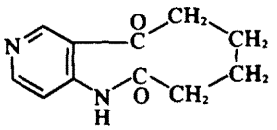
The IR spectrum showed a peak at 1710 cm^{-1} (CO_2H or CO_2CH_3) but did not clearly show the presence of an OH group. Closer inspection of the mass spectrum showed a meta-stable peak at 90·7 due to the transition $p \rightarrow p\text{-}(CH_2)_3 \cdot CO_2H$ and confirming **20** as the structure.

That isolable iodine complexes form with certain

Table 1

1,5-Diazaindene	Chemical shift (δ) H_1	H_2	H_3	H_4	H_6	H_7	Coupling (Hz) $H_{6,7}$
2	11·46	7·45	6·60	8·86	8·18	7·40	5·6
4	11·26	7·04		8·75	8·10	7·26	5·0
20	12·97	7·71		9·60	8·43	8·03	6·8
Methiodide of **2**	12·77	8·03	7·03	9·43	8·50	8·00	7·0
Methiodide of **17**				9·53	8·53	7·97	7·0

The spectra of **4** and the methiodide of **17** were measured in $CDCl_3$ and the remainder in d_6-DMSO.



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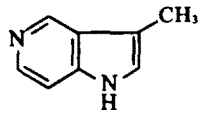

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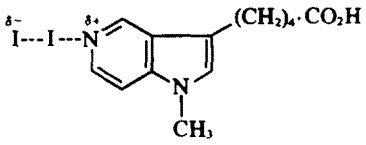

20

1,5-diazaindenes was shown by the precipitation of a complex on mixing ethanolic solutions of iodine and **16**. The NMR spectrum of this product in DMSO was similar to that of **20** and showed downfield shifts of signals compared with those in the spectrum of **16**. Treatment of 1,7-diazaindene (**6**) with iodine in ethanol produced no precipitate, but the NMR spectrum of a mixture of iodine and **6** in DMSO showed a small downfield shift.

Further investigations of the oxidation of diazaindenes, the uses of dimethylsulphonium methylide and the properties of the charge-transfer complexes are in progress.

EXPERIMENTAL

1 - *Acetyl* - 1, 5 - *diazaindene* (1 - *acetyl* - 1H - *pyrrolo* [3,2 - c]*pyridine*), 3. 1,5-Diazaindene[10] (1·8 g) and Ac_2O (10 ml) were heated on a boiling water-bath for 2 h. Ac_2O was distilled off under reduced pressure, water (5 ml) was added, and the soln was basified with Na_2CO_3. Extraction with $CHCl_3$ yielded a solid which was crystallised from benzene–light petroleum (b.p. 80–100°) to give 1 - *acetyl* - 1, 5 - *diazaindene* (2·1 g, 89%), m.p. 98–9° (Found: C, 67·6; H, 4·89; N, 17·2. $C_9H_8N_2O_3$ requires: C, 67·5; H, 5·00; N, 17·5%), ν (KBr) 1709 (CO), δ ($CDCl_3$) 8·83 (1H, s, 4-H), 8·48 (1H, d, 6-H), 8·20 (1H, d, 7-H), 7·43 (1H, d, 2-H), 6·67 (1H, d, 3-H), 2·63 (3H, s, CH_3), $J_{6,7} = 6·1$, $J_{2,3} = 3·9$ Hz.

1 - *Acetyl* - 1, 7 - *diazaindene* (1 - *acetyl* - 1H - *pyrrolo* [2,3-b] *pyridine*), 7. 1,7-Diazaindene[10] (1·4 g) was similarly converted into 1 - acetyl - 1, 7 - diazaindene and after crystallisation from benzene yielded 9·3 g (82%), m.p. 65–66° (lit,[11] 67°).

4 - *Aminonicotinic acid.* 1 - Acetyl - 1, 5 - diazaindene (1·3 g) was added to a mixture of H_2O_2 (30%, 0·8 ml) and glacial AcOH (5 ml) and maintained at 60–70° for 3 h. A further 0·6 ml of peroxide was then added and the soln maintained at 70–80° for 5 h. The solvent was distilled off under reduced pressure and the residue crystallised from aqueous EtOH (charcoal) to give 4-aminonicotinic acid (0·25 g, 22%), m.p. 327–8° (dec) (lit,[12] m.p. 330° (dec)) (Found: C, 52·1; H, 4·51; N, 20·0; *m/e* 138. $C_6H_6N_2O_2$ requires: C, 52·2; H, 4·35; N, 20·3% *m/e* 138), ν (KBr) 3298 and 3149 (NH_2), 2599 (OH), 1651 (CO).

2-*Aminonicotinic acid.* 1 - Acetyl - 1, 7 - diazaindene (1·1 g) was treated in a similar manner to that described for the 1,5-diazaindene isomer to afford a residue, which on crystallisation from EtOH gave 2-aminonicotinic acid (0·19 g, 20%), m.p. 307–8° (dec) (lit,[12] 310° (dec)), ν (KBr) 3270 (NH_2), 2465 (OH), 1700 (CO).

3 - *Acetyl* - 4 - *aminopyridine*, 9. 2, 3 - Dimethyl - 1, 5 - diazaindene[13] (1·0 g), glacial AcOH (5 ml) and H_2O_2 (30%, 1 ml) were heated at 60–70° for 4 h. More peroxide (0·7 ml) was added and the temp maintained at 60–70° for a further 6 h. The solvent was distilled off under reduced pressure, water was added to the residue and the mixture was basified with NaOH aq. The precipitated 2, 3 - dimethyl - 1, 5 - diazaindene (0·43 g) was filtered off and the alkaline filtrate was continuously extracted with $CHCl_3$. The extract yielded a solid which was recrystallised from benzene to give 3 - *acetyl* - 4 - *aminopyridine* (0·12 g, 13%), m.p. 165–166° (Found: C, 61·9; H, 5·83; N, 21·0. $C_7H_8N_2O$ requires: C, 61·8; H, 5·88; N, 20·6%), ν (KBr) 3455 and 3145 (NH_2), 1635 (CO), δ ($CDCl_3$) 8·85 (1H, s, 2-H), 8·12 (1H, d, 6-H), 6·93 (2H, s, which disappears on addition of D_2O, NH_2), 6·53 (1H, d, 5-H), 2·63 (3H, s, CH_3), $J_{5,6} = 6·0$ Hz.

1 - *Acetyl* - 6, 7, 8, 9 - *tetrahydro* - γ - *carboline*, 15. Ac_2O (125 ml) and 6, 7, 8, 9 - tetrahydro - γ - carboline[13] (25 g) were heated on a water-bath for 2 h. The soln was cooled in ice, and the ppt filtered off. Crystallisation from benzene gave 1 - *acetyl* - 6, 7, 8, 9 - *tetrahydro* - γ - *carboline* (25 g, 81%), m.p. 152·5–154° (Found: C, 72·7; H, 6·51; N, 12·7 $C_{13}H_{14}N_2O$ requires: C, 72·8; H, 6·54; N, 13·1%), ν (KBr) 1709 (CO) cm^{-1}, δ ($CDCl_3$) 8·58 (1H, s, 5-H), 8·32 (1H, d, 3-H), 7·73 (1H, d, 2-H), 2·87 (2H, m, CH_2), 2·58 (2H, m, CH_2), 2·58 (3H, s, $COCH_3$), 1·81 (4H, m, $(CH_2)_2$).

6 - (4 - *Aminopyrid* - 3 - *yl*) - 6 - *oxohexanoic acid*, 10. Glacial AcOH acid (4 ml), H_2O_2 (30%, 0·75 ml) and 6, 7, 8, 9 - tetrahydro - γ - carboline[13] (1·0 g) were heated at 70–80° for 4 h. Additional peroxide (0·3 ml) was added and the heating continued for 4 h. After cooling, the ppt was filtered off and crystallised from EtOH as 6 - (4 - *aminopyrid* - 3 - *yl*) - 6 - *oxohexanoic acid* (0·38 g, 30%), m.p. 193–4° (Found: C, 59·1; H, 6·23; N, 12·4; *m/e* 222·1007. $C_{11}H_{14}N_2O_3$ requires: C, 59·4; H, 6·31; N, 12·6%; *m/e* 222·1007), ν (KBr) 3425 and 3198 (NH_2), 1660 (CO) cm^{-1}, δ (d_6-DMSO) 8·80 (1H, s, 2-H), 8·07 (1H, d, 6-H), 7·74 (2H, s which disappears on addition of D_2O, NH_2), 7·5–6·2 (1H, broad s which disappears on addition of D_2O, OH), 6·68 (1H, d, 5-H), 3·00 (2H, m, CH_2), 2·26 (2H, m, CH_2), 1·60 (4H, m, $(CH_2)_2$), $J_{5,6} = 3·0$ Hz.

Addition of Na_2CO_3 aq to the residue from evaporation of the aqueous filtrate yielded 6, 7, 8, 9 - tetrahydro - γ - carboline (0·4 g). Treatment of 1 - acetyl - 6, 7, 8, 9 - tetrahydro - γ - carboline in a similar manner also gave **11** (16%).

3 - *Methyl* - 1, 5 - *diazaindene* (3 - *methyl* - 1H - *pyrrole* [3,2-c]*pyridine*), 4. A soln of dimethylsulphonium methylide was prepared as follows: Dimethylsulphoxide (20 ml) was added to sodium hydride (from 1 g of a 50% mineral oil suspension after separation of the hydride from the oil after the addition of dry light petroleum) and the mixture heated to 70–75° and stirred for 30 min. The soln was cooled to room temp, dry THF (20 ml) was added, and the soln then cooled to −5°. Trimethylsulphonium iodide[14] (2·04 g) in DMSO (25 ml) was added to the stirred soln and the temp maintained below 5°.

3 - Acetyl - 4 - aminopyridine (0·8 g) in DMSO (10 ml) was added to the stirred soln of the ylide with the temp below 0°. The stirred mixture was maintained below 0° for 5 min and then the temp was allowed to rise to room temp. DMSO was distilled off under reduced pressure and water

(5 ml) was added to the cooled residue. The aqueous soln was extracted with ether to give 3 - methyl - 1, 5 - diazaindene (0·12 g, 20%) which was recrystallised from benzene, m.p. 143–4° (lit,[15] m.p. 144–5°), ν (KBr) 3150 (NH), δ ($CDCl_3$) 9·70 (1H, s which disappears on addition of D_2O, NH), 8·93 (1H, s, 4-H), 8·30 (1H, d, 6-H), 7·27 (1H, D, 7-H), 7·04 (1H, s, 2H), 2·40 (3H, s, CH_3), $J_{6,7}$ 4·1 Hz.

4 - (1 - *Methyl* - 1, 5 - *diazainden* - 3 - *yl)butanoic acid–iodine complex* [4-(1-*methyl*-1H-*pyrrolo* [3, 2-c *pyridine* - 3 - *yl)butanoic acid–iodine complex*], **20**. The K salt of 6 - (4 - aminopyrid - 3 - yl) - 6 - oxohexanoic acid (1·1 g) in DMSO (25 ml) was added dropwise to a stirred soln of the ylide, similar to the one described above, maintained at below 5°. The soln was then allowed to come to room temp and stirring was continued until all the solid had dissolved. The solvent was distilled off under reduced pressure and water was added to the cooled residue. Acidification to pH 2 with conc HCl gave a dark solid (1·48 g, 76%), which was recrystallised several times from EtOH (charcoal) as black 4 - (1 - *methyl* - 1, 5 - *diazainden* - 3 - *yl)butanoic acid–iodine complex*, m.p. 146–147° (Found: C, 31·8; H, 3·23; N, 5·7; I, 52·4. $C_{13}H_{16}N_2O_2I_2$ requires: C, 32·1; H, 3·29; N, 5·8; 52·3%), *m/e* 254 and 232·1214 (I_2 and $C_{13}H_{16}N_2O_2$ require 254 and 232·1212 respectively), ν (KBr) 3100, 2960, 1710 (CO) cm^{-1}, δ (d_6-DMSO) 12·97 (1H, s [which undergoes exchange with D_2O], NH), 9·60 (1H, s, 4-H), 8·43 (1H, d, 6-H), 8·08 (1H, d, 7-H), 7·71 (1H, s, 2-H), 3·98 (3H, s, CH_3), 2·87 (2H, m, CH_2), 2·30 (2H, m, CH_2), 1·67 (4H, m, $(CH_2)_2$), $J_{6,7}$ = 6·8 Hz.

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