Chemistry of Heterocyclic Compounds, Vol. 42, No. 5, 2006

OXIDATIVE REACTIONS OF AZINES. 12*. DEHYDROGENATION AND OXIDATION OF 2-METHYL-9-PHENYL-2,3-DIHYDRO-1H-2-AZAFLUORENE

S. V. Volkov, A. N. Levov, O. E. Volkova, N. M. Kolyadina, K. B. Polyanskii, and A. T. Soldatenkov

The oxidation of 2-methyl-9-phenyl-2,3-dihydro-1H-2-azafluorene by air, manganese dioxide, and potassium permanganate has been studied. Depending on the nature of the oxidant it was found that this dihydroazafluorene derivative can be dehydrogenated to the indeno[2,1-c]pyridine anhydro base series, be hydroxylated, oxygenated, or undergo fission to a 2-formamidomethyl-substituted indan-1-one.

Keywords: 2-azafluorene, anhydro base, 2,3-dihydro-1H-2-azafluorene, manganese dioxide, indeno-[2,1-*c*]pyridines, potassium permanganate, dehydrogenation, oxidation.

Continuing our study of the reactions of azafluorenes [2] and the oxidative conversions of heterocyclic compounds containing an allylamine fragment [1, 3] we have turned our attention to the route of oxidation of 2-methyl-9-phenyl-2,3-dihydro-1H-2-azafluorene (**1**) [4]. This azafluorene derivative is an immediate precursor of the antihistamine and anticholinergic drug thephorin and has a diarylaminoalkylmethane structural fragment which is a so called "magic" pharmacophoric group [5].

In this connection, the chemical modification of the molecule **1** is an important undertaking in increasing the potential biological activity of derivatives based on it.

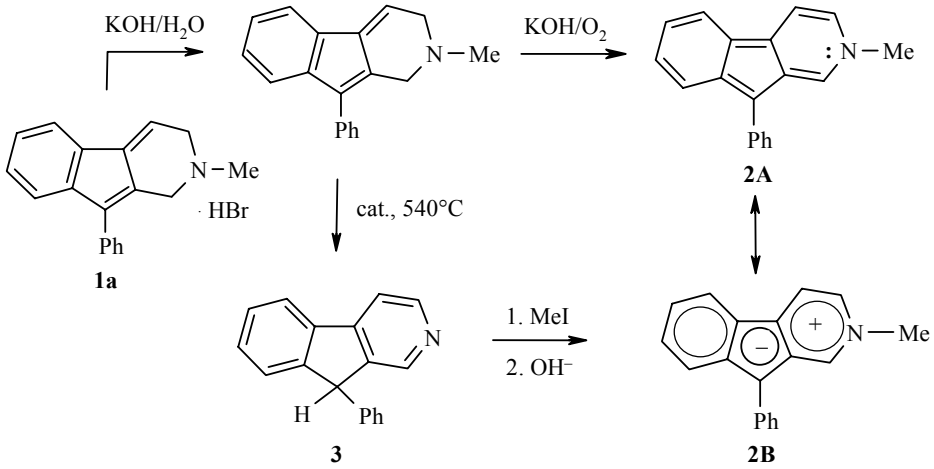
In this work we report the oxidation and dehydrogenation of the starting compound **1** using air, manganese dioxide, and permanganate anion. Since the free base **1b** is of low stability it is usually prepared and stored as the hydrobromide **1a**, basification of which is carried out immediately before the experiment. However, we have noted that prolonged stirring of a suspension of the salt **1a** in a mixture of aqueous base and benzene with passage of air causes gradual colorizing of the organic layer to dark-blue and then to formation of a black precipitate. Analysis of the black-blue crystals obtained showed that, in this case, besides the base **1b** there is formed as side product the high melting anhydro base **2** in 8% yield (Table 1) which has a benzoannelated pseudoazulene structure.

The ^{1}H NMR spectrum (Table 2) shows the absence of the signals for methylene protons at C-1 and C-3 (in the spectrum of the hydrogenated derivative they absorb as a doublet at 3.68 and singlet at 3.41 ppm respectively). To low field there are found two doublet signals at 7.15 and 8.55 ppm with a spin-spin coupling of 4.9 Hz and one singlet at 7.39 ppm having integrated intensities of 1H each and assigned to protons H-3,4 and

* For Communication 11 see [1].

Russian Peoples Friendship University, Moscow 117198; e-mail: swelfen@mail.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 724-730, May, 2006. Original article submitted September 30, 2004.

 0009-3122/06/4205-0636



H-1 respectively and this points to a conversion of the heterocyclic fragment to a 1,4-dihydropyridine of quinoid type (**2A** form). The mass spectrum of compound **2** (Table 3) shows a maximum intensity peak at *m/z* 257 for the molecular ion. The ion peak with *m/z* 242 corresponds to the $[M\text{-}Me]^+$ fragment. A pseudoazulene structure for this compound is confirmed by the mass spectroscopic peaks for double charged ions (with *m*/2*z* 127.5 and 121) which are typical of cyclopenta- and indenopyridine series anhydro bases [6]. The previous formation of the anhydro base **2** was registered only qualitatively in [7] by recording the electronic absorption spectrum of a hexane extract obtained after treatment of the dihydroazafluorene salt **1a** with sulphur at 200°C and subsequent basification of the reaction mixture. For additional structural confirmation of the pseudoazulene **2** we have carried out a thermocatalytic aromatization of compound **1b** in the vapor phase (540°C) with the use of the industrial catalyst K-16 (a mixture of metal oxides) [8]. The 9-phenyl-2-azafluorene (**3**) was prepared (12% yield) and its iodomethylate was converted to the pseudoazulene **2** by the action of base. The spectroscopic data and melting point (a mixed sample did not show a depression of the melting point) for the anhydro base obtained by a counter synthesis proved identical for both samples. It should be noted that the anhydro base **2** is fully stable upon storage as crystals in the absence of air and light. However, it is rapidly decolorized by the action of acid due to the conversion of the zwitterionic 10π-electronic form **2B** to the 8π-pyridinium system [6].

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
2	$C_{19}H_{15}N$	88.34 / 88.72	5.92 / 5.84	5.74 / 5.45	212-215 (with decomp.)	8
3	$C_{18}H_{13}N$	88.68 / 88.89	5.42 / 5.35	5.90 / 5.76	122-124	12
4	$C_{19}H_{15}NO_2$	78.67 / 78.89	5.25 / 5.19	4.98 / 4.84	132-135 (with decomp.)	41
5	$C_{19}H_{15}NO_2$	78.64 / 78.89	5.24 / 5.19	4.97 / 4.84	143-145 (with decomp.)	20
6	$C_{19}H_{15}NO_2$	78.65 / 78.89	5.24 / 5.19	4.97 / 4.84	156-159 (with decomp.)	3
7	$C_{19}H_{19}NO_2$	77.68 / 77.82	6.52 / 6.48	4.83 / 4.78		5
8	$C_{19}H_{13}NO_2$	79.32 / 79.44	4.61 / 4.53	4.91 / 4.88	158-160	8.5
9	$C_{18}H_{15}NO_2$	77.71 / 77.98	5.50 / 5.42	5.12 / 5.05	52-54	6

TABLE 2. ^{1}H NMR Spectra for the Compounds Synthesized **1-9**

Compound	Chemical shift, δ, ppm (spin-spin coupling, *J*, Hz)*					
	H-1	N–CH_3 (3H, s)	H-3	H-4	H apom.	OH
1b	3.68 (2H, s)	2.49	3.41 (2H, d, *J* = 4.0)	6.87 (1H, t, *J* = 4.0)	7.22 (1H, t, *J* = 7.3, H-7); 7.28 (1H, t, *J* = 7.2, H-6); 7.40-7.53 (6H, m); 7.63 (1H, d, *J* = 7.2, H-5)	—
2	7.39 (1H, s)	2.21	7.15 (1H, d, *J* = 4.9)	8.55 (1H, d, *J* =4.9)	7.40-7.64 (9H, m)	—
3	8.77 (1H, s)	—	8.91 (1H, d, *J* = 5.8)	8.61 (1H, d, *J* = 5.8)	7.14-7.61 (8H, m); 8.36 (1H, dd, *J* = 6.4 and *J* = 1.5)	—
4	3.32 (1H, br. s)	3.34	—	6.72 (1H, s)	7.27-7.46 (8H, m); 7.69 (1H, m)	3.44 (1H, br. s, 1-OH)
5	7.62 (1H, s)	3.37	—	6.86 (1H, s)	7.19-7.33 (6H, m); 7.41 (2H, d, *J* = 7.1); 7.90 (1H, d, *J* = 7.3, H-5)	6.40 (1H, br. s, 9-OH)
6	—	3.07	3.04 (1H, br. s)	6.53 (1H, br. s)	7.28-7.50 (8H, m); 7.57 (1H, d, *J* = 7.2, H-5)	3.50 (1H, br. s, 3-OH)
7	3.37 (2H, s)	2.50	2.75 (2H, m)	2.80 (1H, m)	7.05-7.68 (9H, m)	2.20 and 2.70 (1H each, br. s)
8	—	3.30	—	6.77 (1H, s)	7.40-7.72 (9H, m)	—
9[*2]	—	2.65 (2H, s) and 2.82 (1H, s)	—	—	7.08-7.60 (9H, m)	—

* Spectra of compounds **3,5** obtained in DMSO-d_6. In the spectrum of compound **3** the H-1 proton appears as a singlet at 5.68 ppm (1H).

*[2] δ, ppm: 4.14 (1.33H, s, NCH_2); 4.35 (0.67H, s, NCH_2); 7.89 (0.33H, s, HCO) and 8.03 (0.66H, s, HCO).

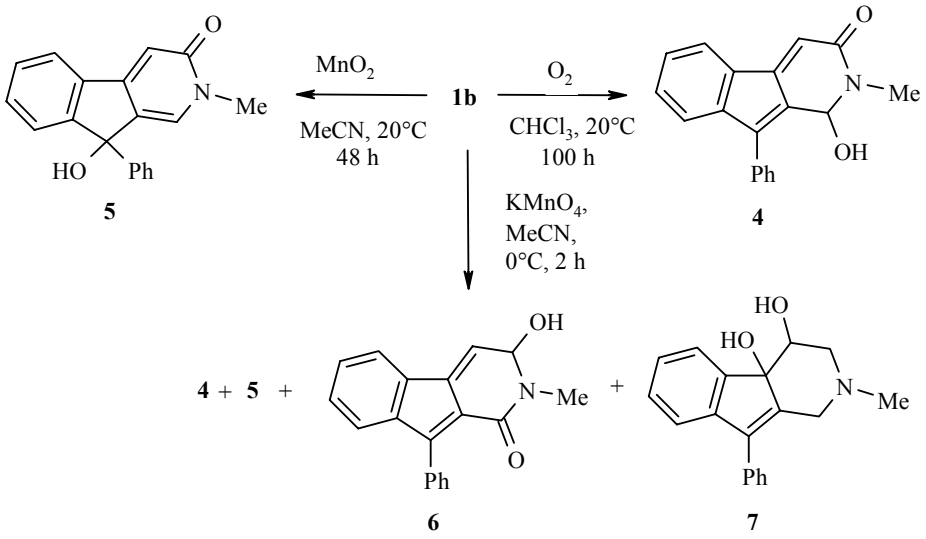
TABLE 3. Mass Spectra of Compounds **2-6, 8, 9**

Compound	*m/z* (I_{rel}, %)*
2	257 $[M]^+$ (100), 242 $[M–Me]^+$ (48), 241 (29), 240 (22), 213 (15), 129 (31), 128.5 $[M]^{2+}$ (50), 121 (10), 116 (9)
3	243 $[M]^+$ (100), 242 $[M–H]^+$ (18), 241 (12), 240 (6), 215 (10), 213 (8), 189 (3), 166 $[M–Ph]^+$ (6), 139 (4)
4	289 $[M]^+$ (69), 273 (50), 272 $[M–OH]^+$ (96), 260 (17), 244 (18), 212 $[M–Ph]^+$ (100), 202 (19), 196 (20), 77 (38)
5	289 $[M]^+$ (42), 273 (28), 272 $[M–OH]^+$ (68), 260 (7), 244 (14), 212 $[M–Ph]^+$ (100), 202 (28), 189 (21), 165 (13), 77 (44)
6	289 $[M]^+$ (59), 273 (18), 272 $[M–OH]^+$ (65), 260 (5), 244 (4), 212 $[M–Ph]^+$ (100), 202 (10), 105 (12), 77 (21)
8	287 $[M]^+$ (80), 286 (100), 259 $[M–CO]^+$ (25), 231 $[M–2CO]^+$ (33), 202 $[M–NMe(CO)_2]^+$ (37), 105 (85), 101 (50), 95 (45), 77 (63), 43 (55)
9	277 $[M]^+$ (0), 274 (18), 249 $[M–CO]^+$ (23), 248 $[M–CHO]^+$ (100), 243 (50), 234 (21), 220 (31), 219 (27), 218 (23)

* [M] and the 8 strongest peaks are given.

Hence it has been shown for the first time that prolonged contact of a basic solution of the 2,3-dihydro-1H-2-azafluorene **1b** with air gives a stepwise oxidative dehydrogenation to form the indenopyridine series anhydro base which has the pseudoazulene fragment and is more stable under these conditions.

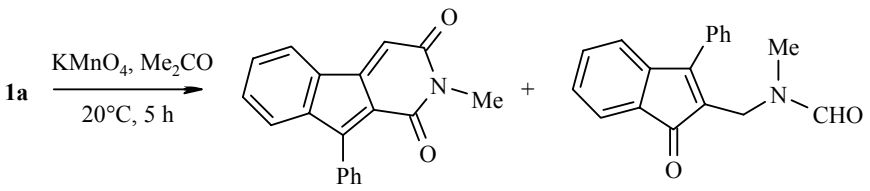
In this connection it was important to determine the oxidative route for the low stability anhydro base **1b** in the presence of various oxidizing agents. First the reaction of compound **1b** with induced bubbling of air through its neutral solution in chloroform was studied. The reaction was carried out over one week at room temperature and gave a 41% yield of the hydroxylated lactam **4**, the structure of which was proved by mass spectrometry and also by ^{1}H NMR.



The oxidation of the 3-CH_2 group to a carbonyl was indicated first by the low field shift of the N-methyl group proton signal ($\Delta\delta$ = 0.85 ppm when compared with the starting material) and secondly by the singlet appearance for the signal of the H-4 proton at 6.72 ppm (in the spectrum of the starting material it appears as a triplet). Proton H-1 gives a broad singlet at 3.32 ppm and the OH group a broad singlet at 3.44 ppm.

Another route for the oxidation of compound **1b** was revealed in the action of manganese dioxide in acetonitrile at 20°C. The use of these conditions led to formation of a complex mixture of products from which the 9-hydroxy-2-methyl-2,3-dihydro-2-azafluoren-3-one (**5**) could be separated in 20% yield. A further decrease in the oxidative selectivity was seen upon changing to the use of potassium permanganate. Thus under Wagner reaction conditions the complex reaction mixture could be separated chromatographically to give low yields (2-5%) of the three isomeric lactams **4-6** and the product of *cis* dihydroxylation **7** (the structure of which was proved from ^{1}H NMR and mass spectra, see Experimental).

It was also interesting to study the oxidation of the hydroindenopyridine **1** taken as the hydrobromide **1a** using permanganate anion. In this case the reaction mixture yielded the imide **8** (8.5% yield) and also the product of a more fundamental oxidation which was the substituted indanone **9** (yield 6%). The latter can be formed as the result of a cascade oxidation of the piperidine fragment initially to the 3-oxo derivative and then with *cis*-dihydroxylation of the olefine bond to give a lactamdiol which then underwent oxidation fission of the C_β–C_γ bond and loss of one carbon atom [9].



8 **9**

In the ^{1}H NMR spectrum of the indanone **9** the protons of the methyl, methylene, and formyl groups give double singlet signals with the same 2:1 ratio of integrated intensities in each pair. This confirms the presence of an amide group in the molecule, existing in $CDCl_3$ solution as the two cisoid and transoid isomeric forms.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WM-400 (400 MHz) spectrometer using $CDCl_3$ solvent and with TMS as internal standard. Mass spectra were obtained on MAT-112 and MX-1303 instruments with direct introduction of the sample into the ionization chamber and ionization intensity of 70 eV. IR spectra were taken on an IR-75 spectrometer for KBr tablets. Silufol UV-254 TLC plates were used for TLC and revealed using iodine vapor. Column chromatography used Silicagel L 32/63. Compounds **1a** and **1b** were prepared as reported in [4]. The physicochemical and spectroscopic characteristics of the compounds synthesized are given in Tables 1-3.

2-Methyl-9-phenyl-2H-indeno[2,1-*c*]pyridine (2). A mixture of the hydrobromide **1a** (12 g, 35 mmol), KOH (50%, 30 ml), and benzene (50 ml) was stirred at room temperature for 14 days. The precipitated black-blue crystals were filtered off and dried to give compound **2** (0.75 g).

9-Phenyl-9H-2-azafluorene (3). A solution of the indenopyridine **2** (5 g, 19 mmol) in benzene (25 ml) was passed through a contact tube containing the K-16 industrial catalyst (30 g) at 530-550°C for 3 h. The solvent was removed in vacuo and the residue (3.8 g) was treated with HCl (1:1, 30 ml) and extracted with benzene (2 × 30 ml) to remove nonnitrogen compounds. The aqueous layer was basified with NaOH to pH 11 and extracted with benzene. The benzene extract was dried with magnesium sulfate, benzene was distilled off, and the residue (1.1 g) was purified through a silica gel column (1.5 × 40 cm) using ethyl acetate–hexane (1:10) as eluent to give compound **3** (0.55 g) as white crystals. A solution of the azafluorene **3** (0.2 g, 0.8 mmol) and CH_3I (1 g, 7 mmol) in absolute benzene (15 ml) was refluxed for 1 h. The precipitate that separated was washed

with ether and dried to give the azafluorene iodomethylate **3a** (0.15 g, 49%). A suspension of the quaternary salt **3a** (0.15 g, 0.4 mmol) in water (20 ml) was treated with 40% KOH solution. The black colored precipitate formed was separated, washed with water, and dried to give the pseudoazulene **2** (0.06 g, 63%) with melting point and ^{1}H NMR spectra identical to the sample formed as above (mixed samples did not give a depression of melting point).

1-Hydroxy-2-methyl-3-oxo-9-phenyl-2,3-dihydro-1H-indeno[2,1-*c*]pyridine (4). A solution of compound **1b** (0.16 g, 0.62 mmol) in chloroform was stirred for 7 days with gentle bubbling of air (1 ml / min). Distillation of solvent then gave an oily, dark-brownish residue. Addition of ether gave the crystalline brownish substance **4** (0.07 g) with IR spectrum, ν, cm^{-1}: 1670 (C=O), 3400 (OH).

9-Hydroxy-2-methyl-3-oxo-9-phenyl-2,3-dihydro-9H-indeno[2,1-*c*]pyridine (5). A mixture of compound **1b** (0.8 g, 3.09 mmol) and manganese dioxide (0.54 g, 6.18 mmol) in MeCN (10 ml) was stirred at room temperature for 48 h. The MnO_2 was filtered off and washed with acetonitrile (5 ml). Distillation of solvent gave an oily dark-brownish residue which was separated on a chromatographic column using ethyl acetate as eluent to give compound **5** as beige crystals (0.12 g). IR spectrum, ν, cm^{-1}: 1620 (C=O), 3250 and 3400 (OH).

Oxidation of Compound 1b Using Potassium Permanganate. Finely ground potassium permanganate (3.05 g, 19 mmol) was added over 0.5 h to a solution of compound **1b** (5 g, 19 mmol) in acetonitrile (150 ml) with cooling (-5°C). The mixture was stirred for 2 h at 0°C and MnO_2 was filtered off and washed with acetonitrile (20 ml). Vacuum distillation of solvent gave an oily residue which was separated on a silica gel column. Elution with chloroform gave **4,4a-dihydroxy-2-methyl-9-phenyl-2,3,4,4a-tetrahydro-1H-indeno[2,1-*c*]pyridine (7)** (0.3 g) as a viscous oil. IR spectrum, ν, cm^{-1}: 3100, 3400 (br). Elution with acetone then gave compound **4** (0.12 g), compound **5** (0.18 g), and **3-hydroxy-2-methyl-1-oxo-9-phenyl-2,3-dihydro-1H-indeno[2,1-*c*]pyridine (6)** (0.15 g) as yellow crystals. IR spectrum, ν, cm^{-1}: 1640 (C=O), 3400 (OH).

Oxidation of Hydrobromide 1a with Potassium Permanganate. Potassium permanganate (0.46 g, 2.9 mmol) was added portionwise over 0.5 h to a solution of compound **1a** (1 g, 2.9 mmol) in acetone (40 ml) with cooling to -5°C. The mixture was stirred at room temperature for 5 h and MnO_2 was filtered off and washed with hot acetone (3 × 10 ml). After distillation of solvent the oily residue was separated on a silica gel column. Elution with benzene gave **2-methyl-1,3-dioxo-9-phenyl-2,3-dihydro-1H-indeno[2,1-*c*]pyridine (8)** as red-brownish crystals (0.07 g). IR spectrum, ν, cm^{-1}: 1640, 1665, 1690 (C=O). Elution with ether then gave **2-(N-formyl-N-methyl)aminomethyl-1-oxo-3-phenylindene (9)** as yellow-orange crystals (0.05 g). IR spectrum, ν, cm^{-1}: 1650 (NCHO), 1700 (C=O).

REFERENCES

1. A. T. Soldatenkov, K. B. Polyanskii, A. V. Temesgen, N. D. Sergeeva, V. V. Vysotskaya, B. B. Averkiev, M. Yu. Antipin, and N. N. Lobanov, *Khim. Geterotsikl. Soedin.*, 755 (2004).
2. N. S. Prostakov, A. T. Soldatenkov, N. M. Kolyadina, and A. A. Obynochnyi, *Usp. Khim.*, **6**, 131 (1997).
3. A. T. Soldatenkov, A. V. Temesgen, and N. M. Kolyadina, *Khim. Geterotsikl. Soedin.*, 643 (2004).
4. J. T. Plati and W. Wenner, *J. Org. Chem.*, **15**, 209 (1950).
5. A. T. Soldatenkov, N. M. Kolyadina, and I. V. Shendrik, *Principles of the Organic Chemistry of Drugs* [in Russian], Mir, Moscow (2003), pp. 59, 132.
6. A. T. Soldatenkov, N. S. Prostakov, and A. A. Obynochnyi, *Khim. Geterotsikl. Soedin.*, 3 (1995).
7. W. Triebs and J. Beger, *Liebigs Ann. Chem.*, **652**, 212 (1962).
8. G. L. Kotel'nikov, L. V. Strunnikov, V. A. Patanov, and I. G. Arapova, *Catalysts for the Dehydrogenation of Lower Alkanes, Olefines, and Alkylaromatic Hydrocarbons* [in Russian], Central Science Institute for Petroleum Chemistry, Moscow (1978), p. 44.
9. A. T. Soldatenkov, A. V. Temesgen, and I. A. Bekro, *Khim. Geterotsikl. Soedin.*, 1332 (2001).