Furopyridines. XXX [1]. Synthesis and Reaction of Difuro[3,2-*c*:-3',2'-*e*]pyridine, A New Tricyclic Heterocycle

Shunsaku Shiotani*, Seiji Yamaguchi, Masahide Kurosaki, Hajime Yokoyama and Yoshiro Hirai

Department of Chemistry, Faculty of Science, Toyama University, Gofuku 3190, Toyama 930, Japan

Received July 29, 1998

Difuro[3,2-*c*:3',2'-*e*]pyridine **1**, a new tricyclic heteroaromatic, has been prepared for the first time. Bromination of **1** with molecular bromine gave 3-bromo **7**, 8-bromo **7'** and 3,8-dibromo derivative **8**; nitration with fuming nitric acid yielded 2-nitro compound **9**, while nitration with a mixture of fuming nitric acid and sulfuric acid gave 2,7-dinitro derivative **10**; formylation with *n*-butyllithium and dimethylformamide gave 2-formyl **11**, 7-formyl **11'**, and 2,7-diformyl compound **12**. The *N*-oxide **14** of **1** afforded 4-cyano compound **15** by cyanation with trimethylsilyl cyanide, 4-chloro compound **16** by chlorination with phosphorus oxychloride, and 4-acetoxyl compound **17** by acetoxylation with acetic anhydride.

J. Heterocyclic Chem., **36**, 403 (1999).

In previous papers we reported the synthesis and chemical properties of furodipyridines [1,2] as an extention of our research work on the chemistry of furopyridines. Now, we intend to synthesize difuropyridines, new tricyclic heteroaromatics which are expected to be new skeletal moieties of biologically active compounds. Thus, we performed the synthesis of difuro[3,2-*c*:3',2'-*e*]pyridine (**1**), starting from methyl 4-chloro-5-ethoxycarbonylfuro[2,3-*b*]pyridine-2-carboxylate (**2**) [3].

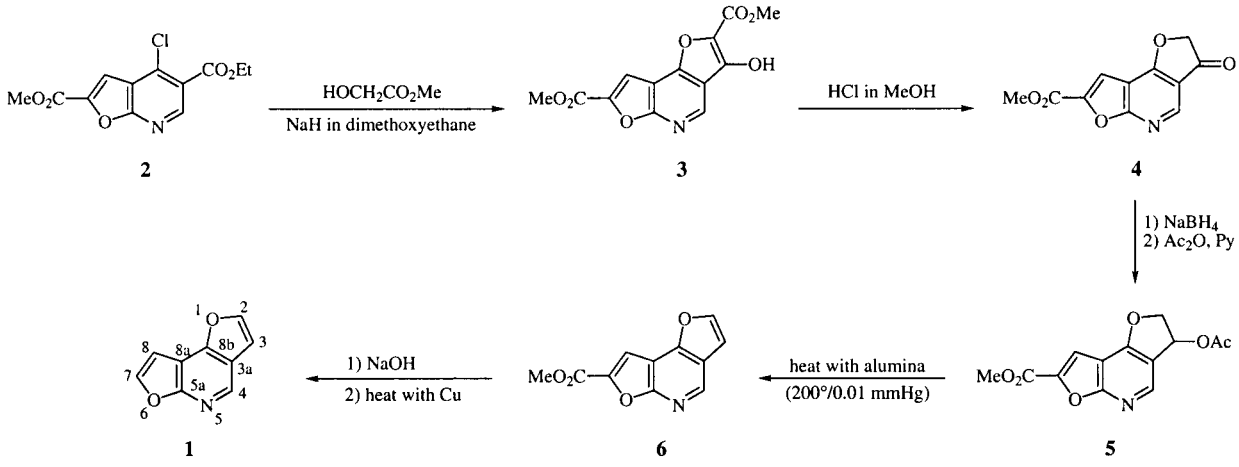
Condensation of compound **2** with sodium methoxycarbonylmethoxide afforded dimethyl 3-hydroxydifuro[3,2-*c*:3',2'-*e*]pyridine-2,7-dicarboxylate (**3**) as colorless crystals of mp 229-234°. The structure of compound **3** was supported by the elemental analysis and data showing an absorption of hydroxyl group in the ir signals of two methoxy methyl in its ^{1}H-nmr spectrum. Reflux of **3** with hydrochloric acid in aqueous methanol gave ketone **4**, which was reduced with sodium borohydride and subsequently acetylated with acetic anhydride to afford 3-acetoxy-2,3-dihydro derivative **5**. When heated with alumina at 200° under reduced pressure, compound **5** yielded the fully aromatic compound **6**. Finally, compound **6** was hydrolyzed and subsequently decarboxylated to give the parent compound **1**.

The ^{1}H-nmr spectrum of compound **1** showed signals of five protons at δ 8.62 (s, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.68 (d, J = 2.2 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H) and 6.96 (d, J = 2.2 Hz, 1H); thus the singlet at δ 8.62 was assigned to the pyridine proton.

Irradiation at δ 7.75 changed the doublet at δ 7.03 to a singlet. This fact indicated that the signals at δ 7.75 and 7.03 and those at δ 7.68 and 6.96 are the pairs of furan moieties respectively.

^{13}C-nmr exhibited nine signals at δ 161.0 (s), 153.8 (s), 144.9 (d), 143.9 (d), 137.8 (d), 120.9 (s), 105.8 (d), 104.8 (s), 102.5 (d) . The ^{1}H-^{13}C COSY spectrum of **1** revealed that the proton at δ 8.62 (the pyridine proton, H-4) is attached to the carbon resonating at δ 137.8 and that the protons at δ 7.75, 7.68, 7.03 and 6.96 are attached to carbons at δ 143.9, 144.9, 102.5 and 105.8 respectively.

Scheme 1



2 **3** **4** **5** **6** **1**

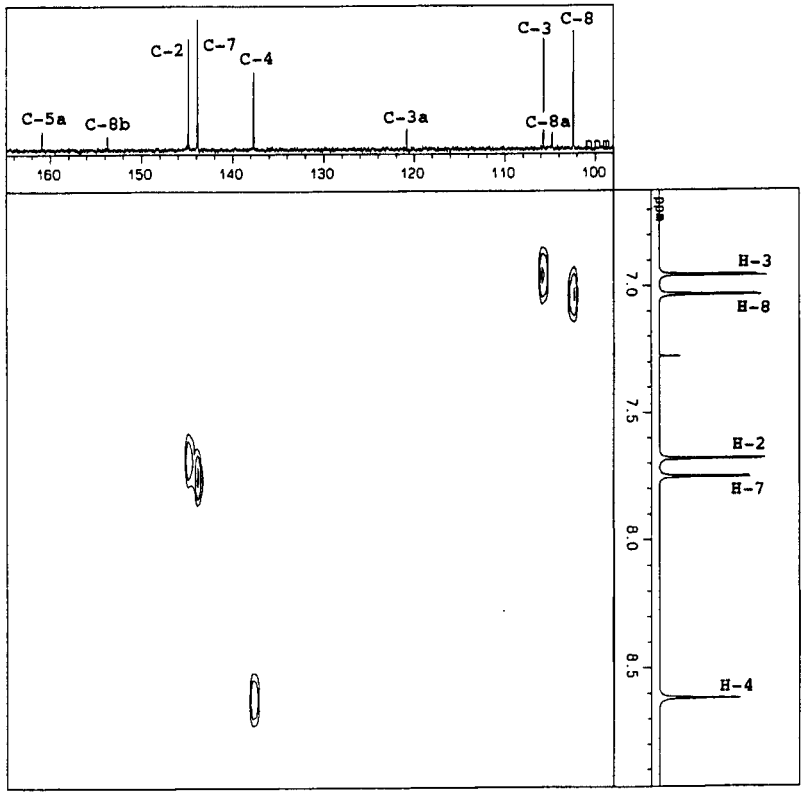


Figure 1. ^{1}H-^{13}C COSY Spectrum of Compound **1**.

Table I

^{13}C Assignments and COLOC Correlations of Compound **1**

Position	^{13}C	COLOC (^{1}H)
2	144.9 (d)	3
3	105.8 (d)	2
3a	120.9 (s)	2,3,4
4	137.8 (d)	
5a	161.0 (s)	4
7	143.9 (d)	8
8	102.5 (d)	7
8a	104.8 (s)	7,8
8b	153.8 (s)	2,3,4

The long-range correlations observed in the COLOC spectrum of **1** provided the evidences for full assignment of the proton and carbon signals. The proton at δ 8.62 (H-4) correlates with carbons at δ 161.0 (s), 153.8 (s) and 120.9 (s). Based on this fact and data of the chemical shifts of C-3a (δ 124.3) and C-7a (δ 158.9) of furo[3,2-*c*]-pyridine and that of C-7a (δ 161.7) of furo[2,3-*b*]pyridine [4], the signal resonating at δ 120.9 is assigned to C-3a (the β-position to the ring nitrogen), the signal at δ 153.8 to C-8b and the signal at δ 161.0 to C-5a. The proton at δ 7.75 (d) correlated with carbons δ 104.8 (s) and 102.5 (d), the proton at δ 7.68 (d) with carbons at δ 153.8 (C-8b), 120.9 (C-3a) and 105.7 (d), the proton at δ 7.03 (d) with carbons at δ 143.9 (d) and 104.8 (s), and the proton at δ 6.96 (d) with carbons at δ 153.8 (C-8b), 144.9 (d) and 120.9 (C-3a), identifying these protons as H-7, H-2, H-8 and H-3 respectively. Thus, the quarternary carbon at δ 104.8 is assigned to C-8a; and the methine carbons at δ 144.9, 143.9, 105.8 and 102.5 are assigned to C-2, C-7, C-3 and C-8 respectively.

Bromination of compound **1** with 1.1 molar equivalents of molecular bromine and the subsequent treatment with sodium hydroxide in methanol afforded 3-bromo- **7** (13%), 8-bromo- **7'** (32%) and 3,8-dibromodifuro[3,2-*c*:-3',2'-*e*]pyridine (**8**) (22%); bromination with 2.0 molar equivalents of bromine gave compound **8** in 89% yield. The structure of compound **8** was confirmed by its elemental analysis indicating the molecular formula $C_9H_3NO_2Br_2$ and the ^{1}H-nmr spectrum showing signals at δ 8.59 (s), 7.82 (s) and 7.78 (s). The position of the bromine atom in the monobromo derivative **7** and **7'** was determined on the basis of ^{1}H- and ^{13}C-nmr spectral data. In the ^{1}H-nmr spectrum, compound **7** showed signals of four protons at δ 8.54 (s, H-4), 7.72 (d), 7.63 (s) and 6.97 (d), and compound **7'** at δ 8.65 (s, H-4), 7.78 (s), 7.77 (d) and 6.99 (d). The ^{13}C-nmr spectrum of **7'** showed signals of nine carbons at δ 159.4 (s), 153.1 (s), 145.7 (d), 141.8 (d), 138.8 (d), 121.8 (s), 105.6 (d and s), 92.6 (s). The

Scheme 2

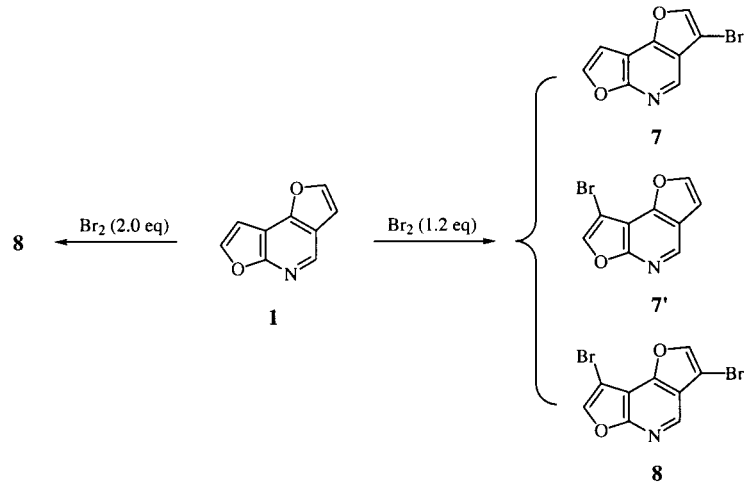


Table II

^{13}C Assignments and HMBC Correlations of Compound **7'**

Position	^{13}C	HMBC (^1H)
2	145.7 (d)	3
3	105.6 (d)	4
3a	121.8 (s)	2,3,4
4	138.8 (d)	
5a	159.4 (s)	4,7
7	141.8 (d)	
8	92.6 (s)	7
8a	105.6 (s)	7
8b	153.1 (s)	2,3,4

HMQC spectrum of **7'** indicated that H-4 (δ 8.65) is attached to carbon resonating at δ 138.8, the proton at δ 7.78 (s) to the carbon at δ 141.8, the proton at δ 7.77 (d) to the carbon at δ 145.7 and the proton at δ 6.99 to the carbon at δ 105.6. In the HMBC spectrum of **7'**, the H-4 correlates with carbons resonating at δ 159.4 (s), 153.1 (s), 121.8 (s) and 105.6 (d), therefore these carbons correspond to C-5a, C-8b, C-3a and C-3 respectively. The proton resonating at δ 7.78 correlates with carbons resonating at δ 159.4 (C-5a), 105.6 (s) and 92.7 (s) identifying the proton as H-7 and the latter two carbons as C-8a and C-8. The proton resonating at δ 7.77 correlates with carbons resonating at δ 153.1 (C-8b) and 121.8 identifying the proton as H-2 and the latter carbon as C-3a. The proton resonating at δ 6.99 correlates with carbons resonating at δ 153.1 (C-8b), 145.7 (d) and 121.8 (C-3a), therefore the proton corresponds to H-3 and the carbon resonating at δ 145.7 to C-2. Thus, the position of bromine atom in **7'** is confirmed at 8-position, and accordingly that in **7** at 3-position.

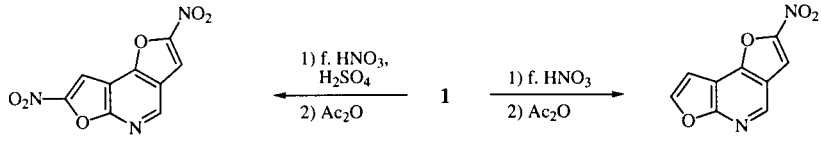
Nitration of **1** with fuming nitric acid and the subsequent treatment with acetic anhydride afforded compound **9** (79%). The structure of **9** was determined on the basis of spectroscopic data. The elemental analysis indicated the molecular formula $C_9H_4N_2O_4$. The ir spectrum showed absorptions for nitro group at 1515 and 1346 cm^{-1}. The ^1H-nmr spectrum of **9** exhibited signals for four protons. A singlet at δ 8.84 was assigned to the pyridine proton (H-4), a pair of doublet at δ 7.90 and 7.18 to the furan protons, and a singlet at δ 7.89 to the proton of the furan nitrated. The ^{13}C-nmr spectrum of **9** showed signals of five quarternary carbons at δ 162.9, 153.0, 151.8, 119.3 and 105.1 and four methine carbons at δ 145.5, 140.8,

Table III

^{13}C Assignments and HMBC Correlations of Compound **9**

Position	^{13}C	HMBC (^1H)
2	153.0 (s)	3
3	106.6 (d)	
3a	119.3 (s)	3,4
4	140.8 (d)	
5a	162.9 (s)	4,7,8
7	145.5 (d)	8
8	102.9 (d)	
8a	105.1 (s)	7,8
8b	151.8 (s)	3,4

Scheme 3



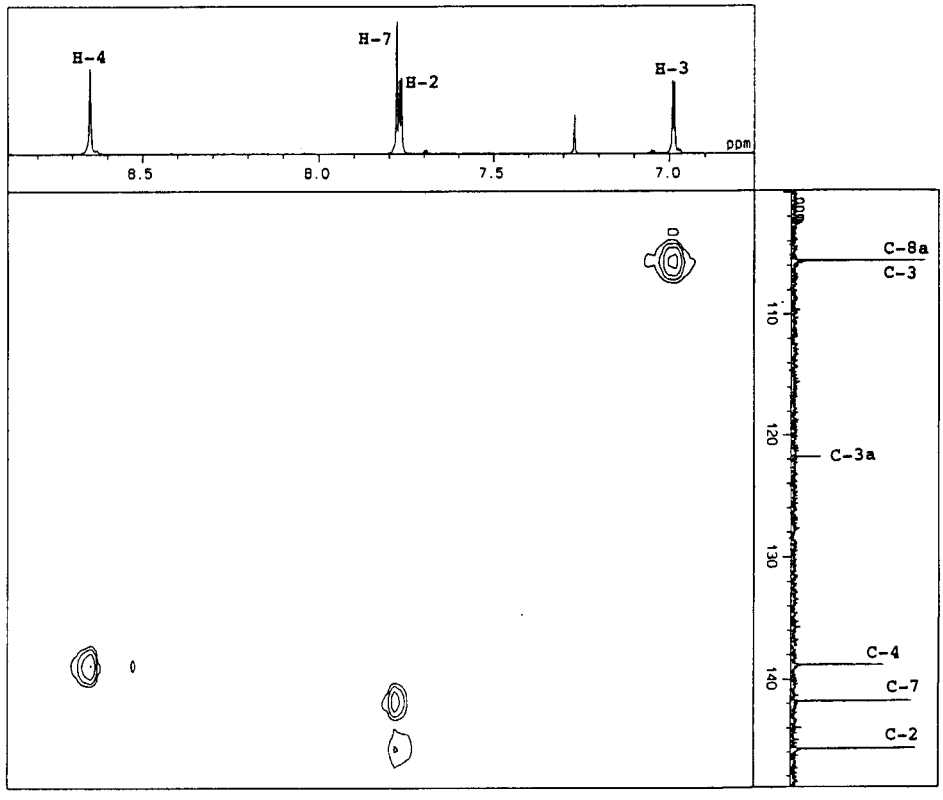


Figure 2. HMQC Spectrum of Compound **7'**.

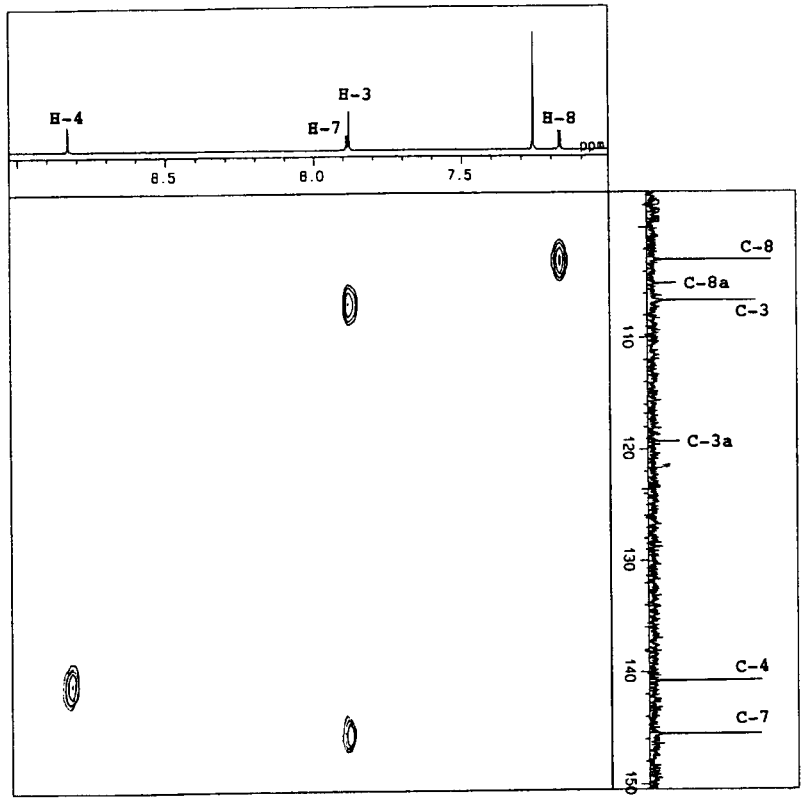


Figure 3. HMQC Spectrum of Compound **9**.

106.6 and 102.9. The HMQC spectrum of **9** indicated that H-4 (δ 8.84) is attached to carbon resonating at δ 140.8, the proton at δ 7.89 (s) to the carbon at δ 106.6, the proton at δ 7.90 (d) to the carbon at δ 145.5 and the proton at δ 7.18 (d) to the carbon at δ 102.9. In the HMBC spectrum of **9**, the H-4 correlates with carbons resonating at δ 162.9 (s), 151.8 (s) and 119.3 (s), therefore these carbons correspond to C-5a, C-8b and C-3a respectively. The proton at δ 7.90 (d) correlates with carbons resonating at δ 162.9 (C-5a) and 105.1 (s) identifying the proton as H-7 and the latter carbon as C-8a. The proton resonating at δ 7.89 (s) correlates with carbons resonating at δ 151.8 (C-8b), 153.0 (s) and 119.3 (s) identifying the proton as H-3 and the latter two carbons as C-2 and C-3a. The proton resonating at δ 7.18 correlates with carbons resonating at δ 162.9 (C-5a), 145.5 (d) and 105.1 (s), therefore the proton corresponds to H-8 and the latter two carbons to C-7 and C-8a. Thus, the position of the nitro group in **9** is confirmed to be 2-position. While, nitration of **1** with a mixture of fuming nitric acid and sulfuric acid yielded 2,7-dinitrodifuro[3,2-*c*:3',2'-*e*]pyridine **10** (67%). The structure of **10** was confirmed from its elemental analysis indicating the molecular formula $C_9H_3N_3O_6$ and ^{1}H-nmr spectrum exhibiting signals of three protons at δ 9.16 (s, H-4), 8.27 (s) and 8.21 (s).

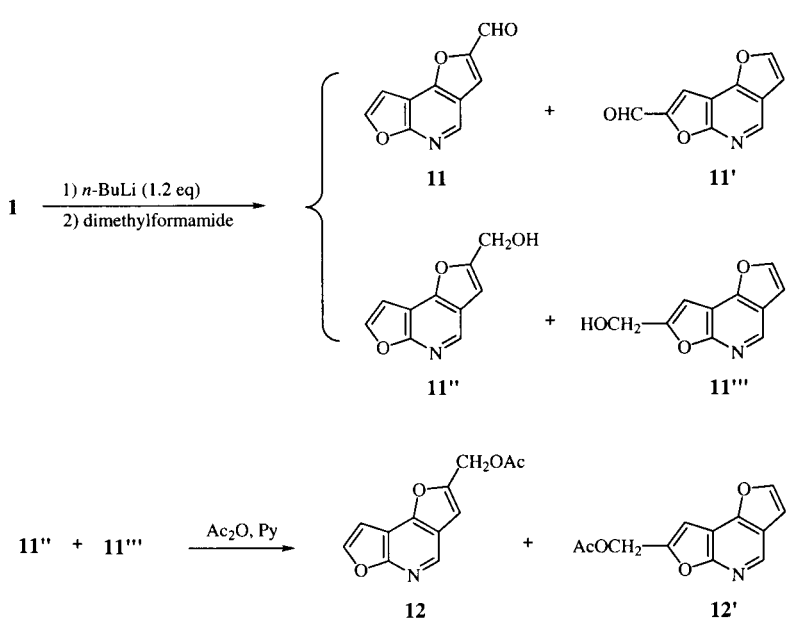
Table IV

^{13}C Assignments and HMBC Correlations of Compound **11'**

Position	^{13}C	HMBC (^{1}H)
2	145.8 (d)	3
3	106.1 (d)	2
3a	121.8 (s)	2,3,4
4	143.1 (d)	
5a	161.0 (s)	4,8
7	151.0 (s)	8
8	110.9 (d)	
8a	105.6 (s)	8
8b	154.6 (s)	2,3,4
-CHO	161.0 (d)	

Formylation of **1** with 1.2 molar equivalents of *n*-butyllithium and dimethylformamide gave a light brown solid mass from which two formyl derivatives, **11** (mp 240-245°) (24%) and **11'** (mp 151-154°) (9%) and a mixture of two hydroxymethyl derivatives were isolated by chromatography on a silica gel column. The mixture of the hydroxymethyl derivatives obtained by the chromatography was acetylated with acetic anhydride and separated by hplc as the acetate **12** and **12'** respectively. The position of the formyl group in compound **11'** was confirmed from its nmr data. The ^{1}H-nmr spectrum of **11'** exhibited signals for five protons. A singlet at δ 9.98 (s) was assigned to the aldehyde proton, a singlet at δ 8.86 (s) was assigned to the pyridine proton (H-4), a singlet at δ 7.79 to the proton of furan formylated, and a pair of doublet at δ 7.78 and 7.04 (J = 2.2 Hz) to protons at another furan ring. The ^{13}C-nmr spectrum of **11'** showed signals for five quarternary carbons at δ 161.0, 154.6, 151.0, 121.8 and 105.6 and five methine carbons at δ 179.9, 145.8, 143.1, 110.9 and 106.1. The ^{1}H-^{13}C COSY spectrum of **11'** indicated that the aldehyde proton (δ 9.98) is attached to carbon resonating at δ 179.9, H-4 (δ 8.86) to carbon resonating at δ 143.1, the proton at δ 7.79 (s) to the carbon at δ 110.9, the proton at δ 7.78 (d) to the carbon at δ 145.8 and the proton at δ 7.04 (d) to the carbon at δ 106.1. In the HMBC spectrum of **11'**, the H-4 correlates with carbons

Scheme 4



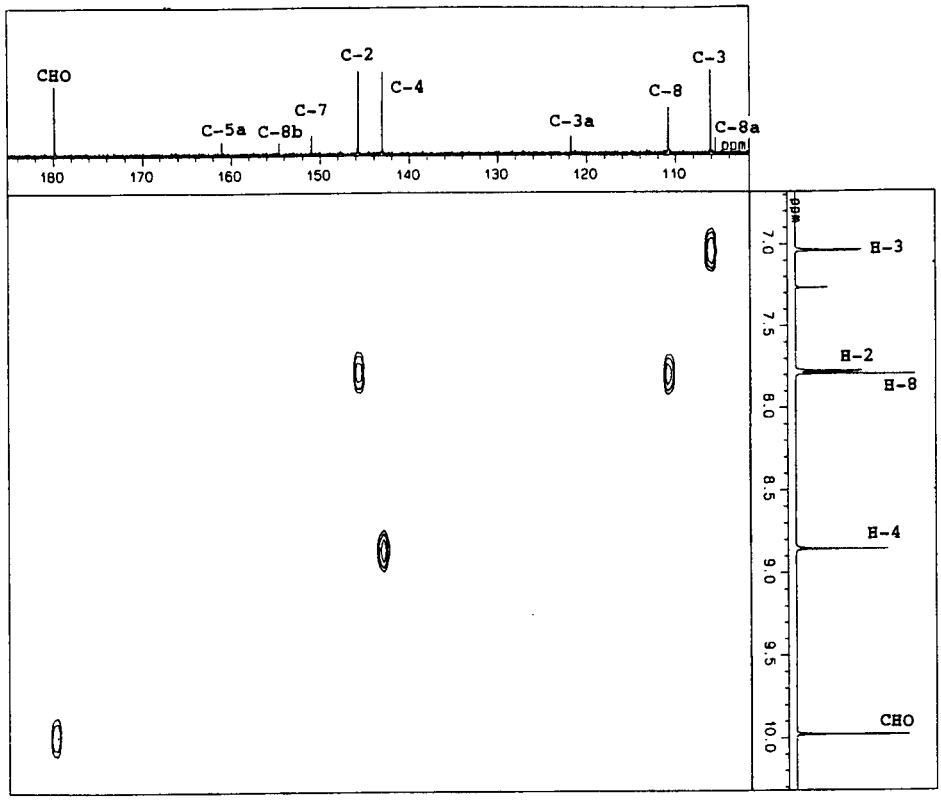
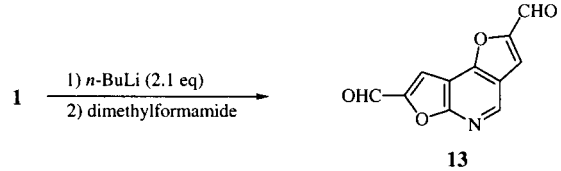


Figure 4. ^{1}H-^{13}C COSY Spectrum of Compound **11'**.

resonating at δ 161.0 (s), 154.6 (s) and 121.8 (s), therefore these carbons correspond to C-5a, C-8b and C-3a respectively. Comparison of the chemical shifts of these carbons with those of C-5a, C-8b and C-3a in the parent compound **1** also supported these assingments. The proton at δ 7.79 (s) correlates with carbons resonating at δ 161.0 (C-5a), 151.0 (s) and 105.6 (s) identifying the proton as H-8 and the carbons as C-7 and C-8a respectively. The proton resonating at δ 7.78 (d) correlates with carbons resonating at δ 154.6 (C-8b), 121.8 (C-3a) and 106.1 (d) identifying the proton as H-2 and the carbons at δ 106.1 as C-3. The proton resonating at δ 7.04 correlates with carbons resonating at δ 154.6 (C-8b), 145.8 (d) and 121.8 (C-3a), therefore the proton corresponds to H-2 and the carbon resonating at 145.8 to C-2. Thus, the position of the formyl group in **11'** was confirmed to be 7-position; therefore, that in **11** 2-position. The formylation with 2.1 molar equivalents of *n*-butyllithium and dimethylformamide gave 2,7-diformyl derivative **13** (30%).

Scheme 5

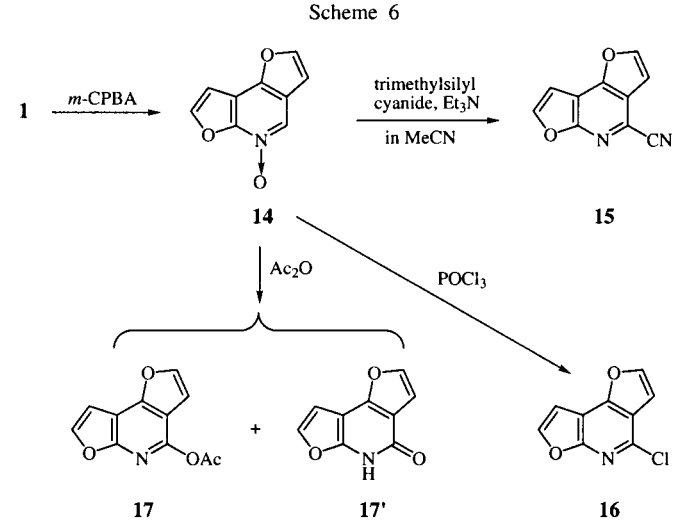


13

Treatment of the difuropyridine **1** with *m*-chloroperbenzoic acid in chloroform at room temperature for 40 hours yielded the *N*-oxide **14** in 51% yield accompanying recovery of **1** (12%).

Cyanation of the *N*-oxide **14** with trimethylsilyl cyanide and triethylamine in acetonitrile afforded 4-cyano compound **15** (58%). Chlorination of **14** with phosphorus oxychloride gave 4-chloro derivative **16** (72%). Acetoxylation of **14** with acetic anhydride gave 4-acetoxy

Scheme 6



14 **15**

17 **17'** **16**

derivative **17** (54%) and difuro[3,2-*c*:3',2'-*e*]pyridin-4(5*H*)-one **17'** (14%). The structures of **15**, **16** and **17** were determined from their ir and ^{1}H-nmr spectra. In the ir spectrum compound **15** showed an absorption of cyano group at 2236 cm^{-1}, and compound **17** a carbonyl absorption of acetate at 1769 cm^{-1}. The ^{1}H-nmr spectra of these compounds exhibited signals of two pairs of doublets assignable to the furan protons (δ 7.97, J = 2.6 Hz, 7.87, J = 2.3 Hz, 7.16, J = 2.3 Hz and 7.15, J = 2.6 Hz for **15**; δ 7.74, J = 2.3 Hz, 7.71, J = 2.3 Hz, 7.02, J = 2.3 Hz and 6.99, J = 2.3 Hz for **16**; δ 7.72, J = 2.3 Hz, 7.67, J = 2.3 Hz, 7.01, J = 2.3 Hz and 6.80, J = 2.3 Hz for **17**) and no signal of the pyridine proton, respectively. Compound **17'** showed a carbonyl absorption of amide at 1659 cm^{-1} and signals of two pairs of the furan protons at δ 7.56 (d, J = 2.4 Hz), 7.45 (d, J = 2.1 Hz), 7.09 (d, J = 2.1 Hz) and 6.89 (d, J = 2.4 Hz).

EXPERIMENTAL

All melting points were determined by using a Yanagimoto micro melting point apparatus and are uncorrected. The ir spectra were recorded on a JASCO FT/IR 7300 spectrometer. The nmr spectra were taken on a JEOL, MAC-FX (90 MHz) and/or JEOL, FX-A400 (400 MHz) instrument in deuteriochloroform, with tetramethylsilane as an internal reference. The nmr spectral assignments were confirmed by spin-decoupling, ^{1}H-^{13}C COSY (512 x 512 data matrix size, 32 scans for **1** and 80 scans for **11'** , interpulse delay 1.300 sec for **1** and 1.4764 sec for **11'**) of **1** and **11'**, HMQC (512 x 512 data matrix size, 2 scans for **7'** and 64 scans for **9**, recycle delay 1.300 sec for **7'** and **9** HMBC (512 x 512 data matrix size, 8 scans, recycle delay 1.300 sec) of **7'**, **9** and **11'** and COLOC (512 x 512 data matrix size, 64 scans, recycle delay 1.300 sec) of **1**. The mass spectra were taken by using JEOL, JMS-OISG-2 instrument. Column chromatography was performed with silica gel (Chromatography Silica Gel BW-820MH, Fuji Silisia Chemical Ltd) or alumina (Merck, Aluminium Oxide 90 Active, Neutral).

Dimethyl 3-Hydroxydifuro[3,2-*c*:3',2'-*e*]pyridine-2,7-dicarboxylate **3**.

To a suspension of sodium hydride (624 mg of 60% dispersion in mineral oil, 15.6 mmoles, washed with hexane) in 1,2-dimethoxyethane (30 ml) was added ethyl glycolate (1.5 g, 16.8 mmoles) during 15 minutes with ice-cooling and stirring. After being stirred for 30 minutes at room temperature, to this mixture was added compound **2** (1.7 g, 6.0 mmoles) in 1,2-dimethoxyethane (20 ml) over a period of 15 minutes. The mixture was stirred and heated at 60-70° for 16 hours. After evaporation of the solvent, the residual solid mass was treated with water, acidified with 10% hydrochloric acid and extracted with chloroform. Drying (magnesium sulfate) and evaporation of the solvent afforded a slightly yellow solid mass, which was recrystallized from methanol-acetone to give 1.6 g (90%) of pure sample of compound **3**, mp 229-234° (colorless crystals); ir (potassium bromide): 3433 (broad), 3219 (broad), 2962, 2925, 2854, 1733, 1672, 1628, 1551, 1472, 1433, 1365, 1322, 1227, 1204, 1189, 1154, 1127, 1088, 1023 cm^{-1}; ^{1}H-nmr: δ 8.93 (s, 1H, H-4), 8.20 (broad s, 1H, OH), 7.78 (s, 1H, H-8), 4.06 (s, 3H, OMe), 4.02 (s, 3H, OMe)

Anal. Calcd. for $C_{13}H_9NO_7$: C, 53.62; H, 3.11; N, 4.81. Found: C, 53.46; H, 3.17; N, 4.80.

Methyl Difuro[3,2-*c*:3',2'-*e*]pyridin-3(2*H*)-one-7-carboxylate **4**.

A mixture of compound **3** (200 mg, 0.69 mmole) and hydrochloric acid (10%, 20 ml) in methanol (40 ml) was refluxed for 30 minutes. After evaporation of the solvent, the residual mass was treated with water, basified with sodium bicarbonate and extracted with chloroform. Drying (magnesium sulfate) and evaporation of the solvent yielded a solid mass. Recrystallization of the solid mass from methanol-acetone gave 97 mg (60%) of pure sample of compound **4**, mp 234-239° (colorless crystals); ir (potassium bromide): 3115, 3070, 2994, 2957, 1731, 1637, 1562, 1471, 1434, 1349, 1303, 1210, 1131, 1103, 1053, 993, 943, 792, 766 cm^{-1}; ^{1}H-nmr: δ 8.81 (s, 1H, H-4), 7.68 (s, 1H, H-8), 4.89 (s, 2H, -CH_2- at 2-position), 4.02 (s, 3H, OMe).

Anal. Calcd. for $C_{11}H_7NO_5$: C, 56.66; H, 3.03; N, 6.01. Found: C, 56.49; H, 3.01; N, 5.84.

Methyl 3-Acetoxy-2,3-dihydrodifuro[3,2-*c*:3',2'-*e*]pyridine-7-carboxylate **5**.

To a stirred solution of ketone **4** (8.4 g, 36.1 mmoles) in methanol (800 ml) was added portionwise sodium borohydride (1.6 g, 43.3 mmoles) with stirring at room temperature. After being stirred for further 1 hour, the solvent was evaporated *in vacuo*. The residue was dissolved in a mixture of pyridine (100 ml) and acetic anhydride (50 ml) and the mixture was stirred at room temperature for 40 hours. After evaporation of the excess acetic anhydride and the pyridine, the residual syrup was treated with water, basified with sodium bicarbonate and extracted with chloroform. Drying (magnesium sulfate) and evaporation of the solvent afforded a solid mass, which was recrystallized from acetone to give 9.5 g (95%) of compound **5**, mp 122-126° (colorless crystals); ir (potassium bromide): 3118, 3070, 3001, 2951, 2924, 2852, 1728, 1644, 1596, 1561, 1485, 1440, 1356, 1290, 1278, 1242, 1202, 1131, 1089, 1053, 939, 829, 764 cm^{-1}; ^{1}H-nmr: δ 8.51 (s, 1H, H-4), 7.53 (s, 1H, H-8), 6.37 (dd, J = 3.5, 5.6 Hz, 1H, H-3), 4.91 (dd, J = 5.6, 11.8 Hz, 1H, H-2a), 4.83 (dd, J = 3.5, 11.8 Hz, 1H, H-2b), 3.99 (s, 3H, OMe), 2.10 (s, 3H, -COMe).

Anal. Calcd. for $C_{13}H_{11}NO_6$: C, 56.23; H, 4.00; N, 5.05. Found: C, 56.44; H, 3.99; N, 5.08.

Methyl Difuro[3,2-*c*:3',2'-*e*]pyridine-7-carboxylate **6**.

A mixture of the acetoxy compound **5** (427 mg, 1.55 mmoles) and alumina (aluminium oxide 90 active, basic, Merck, 430 mg) was heated at 200° for 10 minutes in a glass tube, then the glass tube was evacuated to distil the product at 210-230°/0.01 mm Hg. The distillate was dissolved in chloroform and washed with aqueous solution of sodium bicarbonate. The chloroform solution was dried over magnesium sulfate and evaporated to give 271 mg (81%) of compound **6**, mp 200-204° (colorless crystals); ir (potassium bromide): 3154, 3101, 2961, 2924, 2853, 1720, 1586, 1567, 1443, 1342, 1287, 1209, 1192, 1123, 1086, 1033, 1001, 917, 753 cm^{-1}; ^{1}H-nmr: δ 8.78 (s, 1H, H-4), 7.77 (s, 1H, H-8), 7.74 (d, J = 2.0 Hz, 1H, H-2), 7.01 (d, J = 2.0 Hz, 1H, H-3), 4.01 (s, 3H, OMe).

Anal. Calcd. for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.70; H, 3.06; N, 6.44.

Difuro[3,2-*c*:3',2'-*e*]pyridine **1**.

A solution of the ester **6** (265 mg, 1.25 mmoles), sodium hydroxide (250 mg, 6.25 mmoles) and water (2 ml) in methanol (50 ml) was stirred at room temperature for 1.5 hours. After evaporation of the solvent completely under reduced pressure, the solid residue was pulverized and pyrolized with copper powder (100 mg) using a soft flame in a 5-ml flask equipped with a still head and condenser to give difuropyridine **1** (169 mg, 85%) as colorless crystals, mp 62-67°; ir (potassium bromide): 3162, 3148, 3130, 3106, 3029, 1586, 1523, 1446, 1417, 1341, 1318, 1251, 1151, 1124, 1055, 1024, 907, 873, 805, 744 cm^{-1}; ^{1}H-nmr: δ 8.62 (s, 1H, H-4), 7.75 (d, J = 2.4 Hz, 1H, H-7), 7.68 (d, J = 2.2 Hz, 1H, H-2), 7.03 (d, J = 2.4 Hz, 1H, H-8), 6.96 (d, J = 2.2 Hz, 1H, H-3); ^{13}C-nmr: δ 161.0 (s, C-5a), 153.8 (s, C-8b), 144.9 (d, C-2), 143.9 (d, C-7), 137.8 (d, C-4), 120.9 (s, C-3a), 105.8 (d, C-3), 104.8 (s, C-8a), 102.5 (d, C-8).

Anal. Calcd. for $C_9H_5NO_2$: C, 67.93; H, 3.17; N, 8.80. Found: C, 67.77; H, 3.06; N, 8.80.

Bromination of Difuro[3,2-*c*:3',2'-*e*]pyridine **1**.

(a) To a solution of compound **1** (87 mg, 0.55 mmole) in chloroform was added bromine (97 mg, 0.61 mmole) in carbon tetrachloride (0.5 ml) by syringe at -15° with stirring. After being stirred at this temperature for 10 minutes, the solvents were removed under reduced pressure. The residue was dissolved in methanol (2 ml) containing 10% sodium hydroxide solution (0.5 ml), and the mixture was stirred at room temperature for 10 minutes. The mixture was evaporated, and the residue was treated with water and chloroform. The chloroform layer was dried (magnesium sulfate) and evaporated to give a solid mass, which was chromatographed on a silica gel column eluting with hexane-ethyl acetate (19:1) to give 3-bromo compound **7** (17 mg, 13%), 8-bromo compound **7'** (42 mg, 32%) and 3,8-dibromo compound **8** (39 mg, 22%).

(b) To a solution of compound **1** (97 mg, 0.61 mmole) in chloroform (3 ml) was added bromine (208 mg, 1.3 mmoles) in carbon tetrachloride (0.5 ml) by syringe over a period of 10 minutes at -15°. After the addition was complete, the mixture was stirred for 10 minutes at this temperature. The solvent was removed under reduced pressure at room temperature. The residue was stirred with 10% sodium hydroxide solution (0.5 ml) in methanol (2 ml). After being stirred for 10 minutes at room temperature, the mixture was evaporated to dryness. The residual solid mass was treated with water and chloroform. The chloroform layer was dried (magnesium sulfate) and evaporated to give a solid mass, which was chromatographed on a silica gel column eluting with hexane-ethyl acetate (19:1) to give 173 mg (89%) of dibromo compound **8**.

Compound **7**.

This compound had mp 102-105° (from ether, colorless crystals); ir (potassium bromide): 3159, 3109, 3052, 1584, 1541, 1525, 1444, 1411, 1341, 1314, 1252, 1148, 1101, 1079, 1051, 937, 901, 880, 807, 743 cm^{-1}; ^{1}H-nmr: δ 8.54 (s, 1H, H-4), 7.72 (d, J = 2.3 Hz, 1H, H-7), 7.63 (s, 1H, H-2), 6.97 (d, J = 2.3 Hz, 1H, H-8); ms: m/z (relative intensity) 239 (M^++2, 49), 237 (M^+, 53), 130 (43); hrms: 236.9409. M^+, Calcd. for $C_9H_4NO_2Br$: 236.9425.

Anal. Calcd. for $C_9H_4NO_2Br$: C, 45.41; H, 1.69; N, 5.88. Found: C, 45.62; H, 1.78; N, 5.63.

Compound **7'**.

This compound had mp 117-120° (from ether, colorless crystals); ir (potassium bromide): 3149, 3133, 3041, 1585, 1539, 1445, 1404, 1341, 1302, 1121, 1094, 1034, 1001, 949, 881, 747 cm^{-1}; ^{1}H-nmr: δ 8.65 (s, 1H, H-4), 7.78 (s, 1H, H-7), 7.77 (d, J = 2.2 Hz, 1H, H-2), 6.99 (d, J = 2.2 Hz, 1H, H-3); ^{13}C-nmr: δ 159.4 (s, C-5a), 153.1 (s, C-8b), 145.7 (d, C-2), 141.8 (d, C-7), 138.8 (d, C-4), 121.8 (s, C-3a), 105.6 (s, C-8a and d, C-3), 92.6 (s, C-8); ms: m/z (relative intensity) 239 (M^++2, 82), 237 (M^+, 84), 130 (100); hrms: 236.9419. M^+, Calcd. for $C_9H_4NO_2Br$: 236.9425.

Anal. Calcd. for $C_9H_4NO_2Br$: C, 45.41; H, 1.69; N, 5.88. Found: C, 45.51; H, 1.71; N, 5.60.

Compound **8**.

This compound had mp 124-127° (from acetone-ether, colorless crystals); ir (potassium bromide): 3153, 3142, 3041, 1650, 1583, 1443, 1401, 1343, 1303, 12-75, 1127, 1099, 1080, 1019, 985, 907, 807, 788, 773 cm^{-1}; ^{1}H-nmr: δ 8.59 (s, 1H, H-4), 7.82 (s, 1H, H-7 or H-2), 7.78 (s, 1H, H-2 or H-7).

Anal. Calcd. for $C_9H_3NO_2Br_2$: C, 34.11; H, 0.95; N, 4.42. Found: C, 34.13; H, 1.03; N, 4.37.

Nitration of Compound **1**.

(a) A mixture of difuropyridine **1** (82 mg, 0.52 mmole) in fuming nitric acid (d, 1.50, 1.3 ml) was stirred at 5° for 2.5 hours. The reaction mixture was poured onto ice, neutralized with sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate extract was dried (magnesium sulfate) and evaporated to give a solid mass (118 mg), which was dissolved in acetic anhydride and refluxed for 2.5 hours. After evaporation of the excess of the acetic anhydride under reduced pressure, the syrupy residue was treated with water, basified with sodium bicarbonate and extracted with ethyl acetate. The dried (magnesium sulfate) ethyl acetate extract was evaporated to yield a solid mass, which was chromatographed on a silica gel column eluting with chloroform-methanol (99:1) to give 2-nitro compound **9** (84 mg, 79%).

(b) To a mixture of difuropyridine **1** (70 mg, 0.44 mmole) in sulfuric acid (0.4 ml) was dropwise added a mixture of fuming nitric acid (d, 1.50, 1 ml) and sulfuric acid (0.3 ml) at -5° with stirring. After being stirred for 4.5 hours at room temperature, the reaction mixture was poured on to ice, neutralized with sodium bicarbonate and extracted with ethyl acetate. The ethyl acetate extract was dried (magnesium sulfate) and evaporated to give a yellow solid mass (135 mg), which was dissolved in acetic anhydride (1.5 ml) and refluxed for 3 hours. After evaporation of the excess acetic anhydride, the syrupy residue was treated with water, basified with sodium bicarbonate and extraced with ethyl acetate. The extract was dried (magnesium sulfate) and evaporated to give a solid mass, which was chromatographed on a silica gel column eluting with chloroform-methanol (99:1) to give 73 mg (67%) of 2,7-dinitro compound **10**.

Compound **9**.

This compound had mp 200-205° dec (from acetone, colorless crystals); ir (potassium bromide): 3148, 3128, 3085, 3069, 1645, 1584, 1569, 1515, 1383, 1346, 1258, 1127, 1091, 1056, 1007, 947, 919, 884, 819, 755, '739 cm^{-1}; ^{1}H-nmr: δ 8.84 (s, 1H, H-4), 7.90 (d, J = 2.5 Hz, 1H, H-7), 7.89 (s, 1H, H-3), 7.18 (d, J = 2.5 Hz, 1H, H-8); ^{13}C-nmr: δ 162.9 (s, C-5a), 153.0 (s, C-2), 151.8

(s, C-8b), 145.5 (d, C-7), 140.8 (d, C-4), 119.3 (s. C-3a), 106.6 (d, C-3), 105.1 (s, C-8a), 102.9 (d, C-8).

Anal. Calcd. for $C_9H_4N_2O_4$: C, 52.95; H, 1.97; N, 13.61. Found: C, 52.87; H, 2.09; N, 13.61.

Compound **10**.

This compound had mp 184-187° (from ethanol-ether, pale yellow crystals); ir (potassium bromide): 3150, 3068, 1650, 1585, 1566, 1519, 1441, 1390, 1361, 1326, 1296, 1260, 1249, 1144, 1107, 1087, 958, 948, 859, 811, 780, 734 cm^{-1}; ^{1}H-nmr: δ 9.16 (s, 1H, H-4), 8.27 (s, 1H, H-8 or H-3), 8.21 (s, 1H, H-3 or H-8).

Anal. Calcd. for $C_9H_3N_3O_6$: C, 43.36; H, 1.21; N, 16.87. Found: C, 43.52; H, 1.26; N, 16.90.

Formylation of Compound **1**.

(a) To a solution of compound **1** (110 mg, 0.69 mmole) in tetrahydrofuran (2.5 ml) was added a solution of *n*-butyllithium in hexane (0.52 ml, 1.6*M*, 0.83 mmole) by syringe over a period of 10 minutes under nitrogen atmosphere and stirring at -75°. After being stirred for further 30 minutes at this temperature, the mixture was warmed to -40°, and *N,N*-dimethylformamide (0.11 ml, 1.4 mmoles) was added to this mixture. Then, the cooling bath was removed and the reaction mixture was stirred for 15 hours at room temperature. The mixture was treated with 10% hydrochloric acid and then basified with sodium bicarbonate and extracted with dichloromethane. After drying over magnesium sulfate, the dichloromethane solution was evaporated to leave a solid mass, which was chromatographed on a silica gel (13 g) column eluting with hexane-ethyl acetate (9:1) to give 31 mg (24%) of 2-formyl compound **11**, 12 mg (9%) of 7-formyl derivative **11'** and 18 mg (10%) of a mixture of 2-hydroxymethyl- and 7-hydroxymethyldifuropyridine.

The mixture of hydroxymethyl compounds (12 mg) was dissolved in a mixture of pyridine (1 ml) and acetic anhydride (0.5 ml), and stirred for 48 hours at room temperature. After evaporation of the excess anhydride and pyridine, the residue was treated with water, basified with sodium bicarbonate and extracted with chloroform. Drying (magnesium sulfate) and evaporation of the solvent yielded a colorless syrup, which was separated by using hplc (Hibar column (Merck): LiChromosorb (SiO_2 60)) eluting with hexane-ethyl acetate (85:15) to give 6 mg (41%) of 2-acetoxymethyl compound **12** and 7 mg (48%) of 7-acetoxymethyl compound **12'**.

(b) To a solution of compound **1** (115 mg, 0.72 mmole) in tetrahydrofuran (4 ml) was added a solution of *n*-butyllithium in hexane (0.95 ml, 1.6*M*, 1.5 mmoles) by syringe over a period of 10 minutes under nitrogen atmosphere and stirring at -75°. After being stirred for further 30 minutes at this temperature, the mixture was warmed to -40°, and *N,N*-dimethylformamide (0.12 ml, 1.5 mmoles) was added to this mixture. Then, the cooling bath was removed and the reaction mixture was stirred for 15 hours at room temperature. The mixture was treated with 10% hydrochloric acid and then basified with sodium bicarbonate and extracted with dichloromethane. After drying over magnesium sulfate, the dichloromethane solution was evaporated to leave a solid mass, which was chromatographed on a silica gel column eluting with hexane-ethyl acetate (9:1) to give 47 mg (30%) of 2,7-diformyl compound **13**.

Compound **11**.

This compound had mp 240-245° (from acetone, colorless crystals); ir (potassium bromide): 3147, 3129, 3089, 3027, 1674, 1588, 1521, 1417, 1343, 1293, 1250, 1155, 1127, 1091, 1052, 1017, 932, 882, 823, 786, 768 cm^{-1}; ^{1}H nmr: δ 9.93 (s, 1H, CHO), 8.81 (s, 1H, H-4), 7.84 (d, J = 2.3 Hz, 1H, H-7), 7.76 (s, 1H, H-3), 7.15 (d, J = 2.3 Hz, 1H, H-8).

Anal. Calcd. for $C_{10}H_5NO_3$: C, 64.18; H, 2.69; N, 7.48. Found: C, 64.17; H, 2.67; N, 7.51.

Compound **11'**.

This compound had mp 151-154° (from acetone, colorless crystals); ir (potassium bromide): 3157, 3138, 3109, 3059, 1686, 1639, 1580, 1548, 1450, 1337, 1310, 1278, 1236, 1160, 1127, 1084, 989, 950, 827, 788, 762 cm^{-1}; ^{1}H-nmr: δ 9.98 (s, 1H, CHO), 8.86 (s, 1H, H-4), 7.79 (s, 1H, H-8), 7.78 (d, J = 2.2 Hz, 1H, H-2), 7.04 (d, J = 2.2 Hz, 1H H-3); ^{13}C-nmr: δ 179.9 (d, CHO), 161.0 (s, C-5a), 154.6 (s, C-8b), 151.0 (s, C-7), 145.8 (d, C-2), 143.1 (d, C-4), 121.8 (s, C-3a), 110.9 (d, C-8), 106.1 (d, C-3), 105.6 (s, C-8a).

Anal. Calcd. for $C_{10}H_5NO_3$: C, 64.18; H, 2.69; N, 7.48. Found: C, 63.91; H, 2.74; N, 7.47.

Compound **12**.

This compound had mp 81-86° (from acetone-ether, colorless crystals); ir (potassium bromide): 3137, 3096, 3027, 2920, 2850, 1746, 1650, 1585, 1524, 1376, 1365, 1341, 1311, 1255, 1236, 1139, 1091, 1061, 1021, 970, 921, 818, 701 cm^{-1}; ^{1}H-nmr: δ 8.58 (s, 1H, H-4), 7.76 (d, J = 2.4 Hz, 1H, H-7), 7.04 (d, J = 2.4 Hz, 1H, H-8) 6.96 (s, 1H, H-3), 5.27 (s, 2H, -CH_2-), 2.14 (s, 3H, -COMe); ms: m/z (relative intensity) 231 (M^+, 44), 189 (28), 173 (12), 172 (100), 171 (27); hrms: 231.0540. M^+, Calcd. for $C_{12}H_9NO_4$: 231.0531.

Compound **12'**.

This compound had mp 63-66° (from acetone-ether, colorless crystals); ir (potassium bromide): 3151, 3125, 2923, 2852, 1740, 1646, 1581, 1447, 1360, 1343, 1255, 1234, 1128, 1027, 947, 809, 744 cm^{-1}; ^{1}H-nmr: δ 8.62 (s, 1H, H-4), 7.68 (d, J = 2.4 Hz, 1H, H-2), 7.03 (s, 1H, H-8), 6.96 (d, J = 2.4 Hz, 1H, H-3), 5.27 (s, 2H, -CH_2-), 2.14 (s, 3H, -COMe); ms: m/z (relative intensity) 231 (M^+, 56), 189 (83), 188 (12), 173 (12), 172 (100), 171 (24), 161 (15), 160 (23), 144 (23), 143 (34); hrms: 231.0523. M^+, Calcd. for $C_{12}H_9NO_4$: 231.0531.

Compound **13**.

This compound had mp >300° (from acetone, colorless crystals); ir (potassium bromide): 3123, 3094, 3064, 2886, 2844, 1679, 1640, 1584, 1547, 1377, 1339, 1290, 1171, 1107, 1032, 947, 928, 841, 772 cm^{-1}; ^{1}H-nmr: δ 9.95 (s, 1H, -CHO), 9. 94 (s, 1H, -CHO) , 9.17 (s, 1H, H-4), 8.39 (s, 1H, H-8 or H-3), 8.30 (s, 1H, H-3 or H-8).

Anal. Calcd. for $C_{10}H_5NO_3$: C, 61.40; H, 2.34; N, 6.54. Found: C, 61.25; H, 2.47; N, 6.54.

Difuro[3,2-*c*:3',2'-*e*]pyridine *N*-Oxide **14**.

A mixture of difuropyridine **1** (544 mg, 3.4 mmoles) and *m*-chloroperbenzoic acid (70% purity, 2.5 g, 10.2 mmoles) in chloroform (60 ml) was stirred at room temperature for 40 hours. The mixture was filtered slowly with an alumina (basic, 50 g) pad to remove the acidic components. The filtrate was evaporated to give the *N*-oxide monohydrate **14** (305 mg, 51%) and the starting compound **1** (70 mg, 12%).

Compound **14** had mp 170-174° (from acetone, colorless crystals); ir (potassium bromide): 3445 (broad), 3137, 3105, 3046, 1526, 1463, 1433, 1298, 1246, 1226, 1154, 1122, 1033, 882, 789, 735 cm^{-1}; ^{1}H-nmr: δ 8.60 (s, 1H, H-4), 7.84 (d, J = 2.3 Hz, 1H, H-7), 7.78 (d, J = 2.3 Hz, 1H, H-2), 7.12 (d, J = 2.3 Hz, 1H, H-8), 6.91 (d, J = 2.3 Hz, 1H, H-3).

Anal. Calcd. for $C_9H_5NO_3 \cdot H_2O$: C, 55.96; H, 3.65; N, 7.25. Found: C, 56.01; H, 3.45; N, 7.06.

4-Cyanodifuro[3,2-*c*:3',2'-*e*]pyridine **15**.

To a solution of the *N*-oxide monohydrate **14** (84 mg, 0.44 mmole) in acetonitrile (2 ml) was added triethylamine (0.1 ml, 0.72 mmole) and trimethylsilyl cyanide (0.16 ml, 1.2 mmoles) by syringe under a nitrogen atmosphere with stirring. The mixture was refluxed for 20 hours. After evaporation of the solvent under reduced pressure, the mixture was treated with chloroform and water. The aqueous layer was extracted with chlorofrom. The combined chloroform layers were dried (magnesium sulfate) and evaporated to give a solid mass, which was chromatographed on a silica gel column eluting with hexane-ethyl acetate (4:1) to yield 51 mg (58%) of 4-cyano compound **14**. Recrystallization of **14** from acetone-ether gave the analytically pure sample, mp 122-125° (colorless crystals); ir (potassium bromide): 3151, 3130, 3048, 2236, 1534, 1516, 1424, 1349, 1319, 1280, 1164, 1135, 1113, 1073, 1019, 887, 875, 792 cm^{-1}; ^{1}H-nmr: δ 7.97 (d, J = 2.6 Hz, 1H, H-7), 7.87 (d, J = 2.3 Hz, 1H, H-2), 7.16 (d, J = 2.3 Hz, 1H, H-3), 7.15 (d, J = 2.6 Hz, 1H, H-8).

Anal. Calcd. for $C_{10}H_4N_2O_2$: C, 65.22; H, 2.19; N, 15.21. Found: C, 65.18; H, 2.25; N, 15.09.

4-Chlorodifuro[3,2-*c*:3',2'-*e*]pyridine **16**.

A mixture of the *N*-oxide **14** (112 mg, 0.64 mmole), phosphorus oxychloride (1 ml, 10.9 mmoles) in chloroform (0.5 ml) was refluxed for 1.5 hours. After being cooled, the mixture was poured into ice-water, basified with sodium bicarbonate and extracted with chloroform. The chloroform extract was dried (magnesium sulfate) and evaporated to give a solid mass, which was chromatographed on a silica gel column eluting with hexane-ethyl acetate (4:1) to yield 4-chloro compound **16** (89 mg, 72%). Recrystallization of **16** from ether gave the pure sample, mp 100-104° (colorless crystals); ir (potassium bromide): 3153, 4127, 3043, 1585, 1571, 1519, 1416, 1407, 1342, 1323, 1156, 1127, 1085, 1065, 1018, 1010, 893, 875,783, 737 cm^{-1}; ^{1}H-nmr: δ 7.74 (d, J = 2.3 Hz, 1H, H-7), 7.71 (d, J = 2.3 Hz, 1H, H-2), 7.02 (d, J = 2.3 Hz, 1H, H-8), 6.99 (d, J = 2.3 Hz, 1H, H-3).

Anal. Calcd. for $C_9H_4NO_2Cl$: C, 55.84; H, 2.08; N, 7.24. Found: C, 55.83; H, 2.14; N, 6.92.

4-Acetoxydifuro[3,2-*c*:3',2'-*e*]pyridine **17** and Difuro[3,2-*c*:-3',2'-*e*]pyridin-4(5*H*)-one **17'**.

A solution of the *N*-oxide **14** (107 mg, 0.61 mmole) in acetic anhydride (2 ml) was refluxed for hour. After evaporation of the excess acetic anhydride, the dark brown syrupy residue was treated with water, basified with sodium bicarbonate and extracted with chloroform. The chloroform extract was dried (magnesium sulfate) and evaporated to afford a brown syrup, which was chromatographed on a silica gel column eluting with hexane-ethyl acetate (93:7) to give 72 mg (54%) of 4-acetoxy derivative **17** and 15 mg (14%) of the pyridone compound **17'**.

Compound **17**.

This compound had mp 98-101° (from acetone-ether, colorless crystals); ir (potassium bromide): 3153, 3129, 3117, 3048, 3023, 2924, 2853, 1769, 1660, 1639, 1588, 1535, 1521, 1434, 1418, 1359, 1321, 1298, 1195, 1166, 1140, 1123, 1084, 1032, 893, 871, 789, 751, 723 cm^{-1}; ^{1}H-nmr: δ 7.72 (d, J = 2.3 Hz, 1H, H-7), 7.67 (d, J = 2.3 Hz, 1H, H-2), 7.01 (d, J = 2.3 Hz, 1H, H-8), 6.80 (d, J = 2.3 Hz, 1H, H-3), 2.40 (s, 1H, -OAc).

Anal. Calcd. for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.86; H, 3.34; N, 6.20.

Compound **17'**.

This compound had mp 210-214° (from acetone, colorless crystals); ir (potassium bromide): 3163, 3123, 1659, 1613, 1596, 1482, 1397, 1342, 1308, 1205, 1178, 1151, 1114, 1061, 1019, 877, 720 cm^{-1}; ^{1}H nmr: δ 7.56 (d, J = 2.4 Hz, 1H, H-7), 7.45 (d, J = 2.1 Hz, 1H, H-2), 7.09 (d, J = 2.1 Hz, 1H, H-3), 6.89 (d, J = 2.4 Hz, 1H, H-8); ms: m/z (relative intensity) 176 (M^++1, 13), 175 (M^+, 100), 147 (11), 146 (10), 120 (14), 119 (41); hrms: 175.0272. M^+, Calcd. for $C_9H_5NO_3$: 175.0269.

Anal. Calcd. for $C_9H_5NO_3$: C, 61.72; H, 2.88; N, 8.00. Found: C, 61.58; H, 3.29; N, 8.33.

REFERENCES AND NOTES

[1] Part **XXIX**: S. Yamaguchi, K. Orito, N. Shimizu, K. Taniguchi, H. Saitoh, M. Kurosaki, H. Yokoyama, Y. Hirai and S. Shiotani, *J. Heterocyclic Chem.*, submitted.

[2] S. Shiotani and H. Morita, *J. Heterocyclic Chem.*, **27**, 637 (1990).

[3] M. Bhupathy, D. A. Conlon, K. M. Wells, J. R. Nelson, P. J. Reider, K. Rossen, J. W. Sager and R. P. Volante, *J. Heterocyclic Chem.*, **32**, 1283 (1995).

[4] S. Shiotani and H. Morita, *J. Heterocyclic Chem.*, **28**, 1469 (1991).