Chemistry of Heterocyclic Compounds, Vol. 38, No. 2, 2002

CYCLOADDITION IN CONDENSED ISOINDOLES. 2*. METHOD FOR OBTAINING NEW DERIVATIVES OF 2-PHENYLPYRIDINE

Z. V. Voitenko, A. A. Pokholenko, O. O. Shkarov, V. A. Kovtunenko, and F. S. Babichev

The reaction of pyrido[2,1-a]isoindole with maleimide derivatives has been investigated. A new rearrangement has been found, the products of which are 2-[2'-(1-R-2,5-dioxopyrrolidinidene)-2'-(1-R-2,5-dioxopyrrolidinyl)methyl]phenylpyridines. A probable mechanism for the rearrangement has been proposed. The existence of atropoisomerism for the compounds obtained has been demonstrated by ^{1}H NMR spectra.

Keywords: pyrido[2,1-*a*]isoindole, 2-phenylpyridines, cycloaddition.

Pyrido[2,1-*a*]isoindole (**1**) is a 14 π-electron heteroaromatic system capable of reacting by cycloaddition [2]. Calculations on the electronic structure of compound **1** show that Michael and Diels–Alder reactions are most probable at positions 6 and 6, 10b respectively [3].

In the known examples of the cycloaddition of pyrido[2,1-*a*]isoindoles with dienophiles containing both double and triple bonds [4,5], addition has been described at positions 1,4 or 4,6 and also the formation of Michael adducts at position 6, i.e. the literature data are extremely inconsistent. A single example is also known of the interaction of compound **1** with *p*-tolylmaleimide with the formation of a Michael adduct, *viz*. 6-[1-(*p*-tolyl)succinimidyl]pyrido[2,1-*a*]isoindole (**2b**) [5].

Our attempts to reproduce the reaction of compound **1** with *p*-tolylmaleimide and similar dienophiles under the conditions described in [5] led to a mixture of substances in which, according to ^{1}H NMR data, the presence of 20-30% adducts of type **2** was possible. The main reaction products were substances of type **4** which are readily obtained in a pure state under thermodynamic control of the reaction using a twofold excess of dienophile (Scheme 1).

The structures of compounds **4a-g** were established by results of elemental analysis and spectral data (Tables 1 and 2), and in the case of compound **4a** by X-ray structural analysis as well [6].

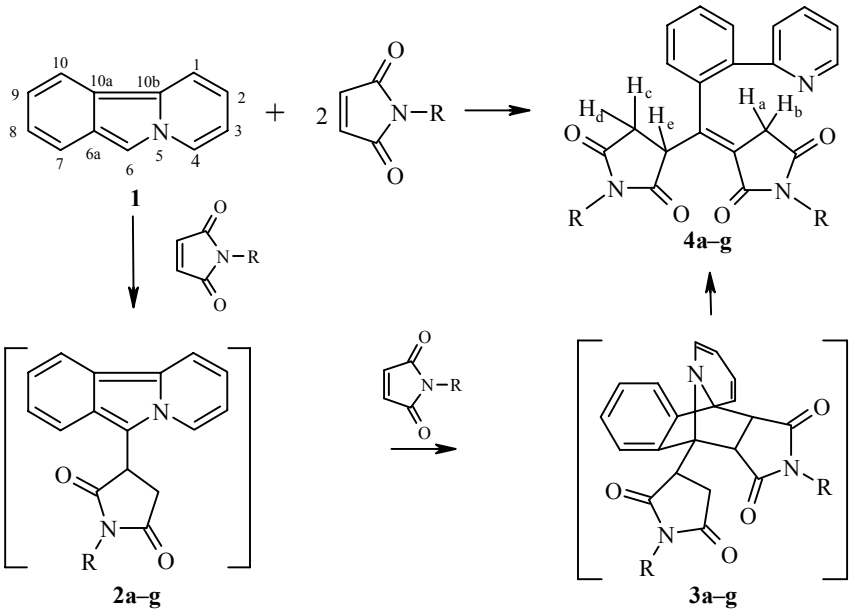
The IR spectra of compounds **4a-g** contain bands for the stretching vibrations of the C=O groups and skeletal vibrations for the aromatic C=C bonds. In the UV spectra of these substances, which were of one type and consistent with the structure proposed, there was an absorption band for the aromatic conjugated chromophores, but the isoindole long-wave absorption characteristic for adducts of type **2** was absent [7]. The ^{13}C and ^{1}H NMR spectra confirm the structure of the compounds obtained (Tables 2-4).

* For Part 1 see [1].

Kiev Taras Shevchenko National University, Kiev 01033, Ukraine; e-mail: zvoitenko@mail.univ.kiev.ua, zvoitenko@hotmail.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii. No. 2, pp. 211-217, February, 2002. Original article submitted December 23, 1999.

 0009-3122/02/3802-0190$27.00

Scheme 1



a R = Ph; **b** R = *p*-MeC_6H_4; **c** R = *p*-$MeOC_6H_4$; **d** R = *p*-$NO_2C_6H_4$;
e R = H; **f** R = CH_2Ph; **g** R = 2-Nph

We propose the following reaction mechanism. In the first stage of the reaction one maleimide molecule adds according to Michael at position 6 of pyrido[2,1-*a*]isoindole, then a second molecule of the dienophile adds to the isoindole formed according to Diels–Alder at positions 6 and 10b, finally adduct **3** is rearranged into compound **4** (Scheme 1) with scission of two bridging bonds (C–C and C–N) in the strained ring, which is energetically profitable as it is accompanied by aromatization of the pyridine ring and the formation of an exocyclic double bond.

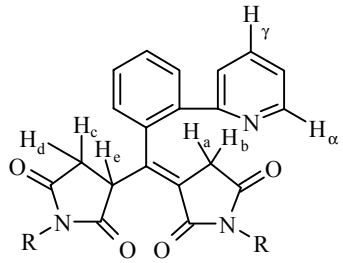
The products **4a-g** of the newly discovered rearrangement recall the compounds described by us previously formed in the reaction of 6-methyl-5,6-dihydroisoindolo[2,1-*a*]quinazolin-5-one with maleimide derivatives [1]. However the differences in carrying out these processes were that only for compound **1** a Michael addition at the first reaction stage was characteristic. This leads to "overloading" of the exocyclic double bond by bulky substituents, formed as a result of the rearrangement.

Some special features of the ^{1}H NMR spectra of the rearrangement products must be mentioned. In the spectrum of compound **4f** the protons of the benzyl group are diastereotopic and are displayed as a superposition of AB systems at 2.69-3.16 ppm (Table 2). Judging by the spectra atropoisomerism is natural for this type of compound. Similar cases of atropoisomerism for compounds with "overloading" of a double bond have been described previously in the literature [8] and were confirmed by our calculations in [9]. In the ^{1}H NMR spectrum of compound **4c** (Table 3) a double number of signals are present for the diastereotopic protons H_a and H_b, H_c and H_d. At higher field the picture of AB systems for the protons H_a and H_b is repeated, there are two doublets for each atropoisomer. The H_c and H_d protons are displayed as two doublets of one of the atropoisomers but in the second atropoisomer these protons are probably completely equivalent and are split only by H_e (see Table 3). The integrated intensity of the H_e signal is reduced relative to the total intensity of the signals of the two aliphatic protons, but near 6 ppm there is a broad signal precisely completing its intensity to the full amount. On the basis of this we proposed that for the 2-phenylpyridines **4a-g** not only atropoisomerism but also tautomerism is a characteristic (see Scheme 2). The enol form is present in compounds **4a,c,d,f** to 30-38%, but the precise ratio of the tautomeric forms was not successfully established for compounds **4b,e,g**.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f	IR spectrum, ν, cm^{-1}		UV spectrum, λ_{max}, nm (log ε)	Yield, %
		C	H	N			C=O	C=C		
4a	$C_{32}H_{23}N_3O_4$	74.23, 74.40 74.84	4.70, 5.07 4.51	7.91, 8.08 8.18	213-215	0.69	1707 s 1765 m	1650 m	312 (2.5522); 296 (2.6905); 264 (3.3815); 256 (3.3734); 247 (3.3023); 237 (3.4272); 231 (3.5064); 222 (3.5734); 221 (3.5734)	94
4b	$C_{34}H_{27}N_3O_4$	74.98, 75.16 75.40	5.29, 5.42 5.03	7.87, 7.44 7.76	212-214	0.69	1705 s 1768 m	1658 m	269 (4.2846); 252 (4.2936); 250 (4.2956); 243 (4.3081); 222 (4.5200)	97
4c	$C_{34}H_{27}N_3O_6$	71.28, 71.10 71.19	5.12, 4.98 4.74	7.60, 7.42 7.33	195-197	0.70	1705 s 1765 m	1650 m	271 (3.9080); 266 (3.9107); 242 (4.1391); 230 (4.2857)	99
4d	$C_{32}H_{21}N_5O_8$	64.01, 63.87 63.68	3.87, 3.94 3.51	11.33, 11.42 11.60	182-185	0.69	1708 s 1770 m	1645 w	287 (3.6548); 276 (3.6851); 251 (3.5602); 247 (3.5254); 234 (3.5765); 225 (3.6637); 224 (3.6681)	96
4e	$C_{20}H_{15}N_3O_4$	66.70, 66.63 66.48	4.42, 4.56 4.18	11.40, 11.72 11.63	204-205	0.52	1705 s 1765 m	1650 m	273 (3.8389); 250 (3.9473); 246 (3.9654); 230 (4.0771); 228 (4.0790); 223 (4.0897)	80
4f	$C_{34}H_{27}N_3O_4$	75.48, 75.55 75.40	5.27, 5.20 5.03	9.40, 9.47 7.76	66-67	0.74	1700 s 1760 m	1655 w	264 (4.1080); 250 (4.1580); 248 (4.1607); 247 (4.1607); 231 (4.2088); 221 (4.2276)	84
4g	$C_{40}H_{27}N_3O_4$	78.92, 79.05 78.29	4.55, 4.62 4.43	8.62, 8.79 6.85	121-122	0.71	1710 s 1765 m	1655 w	293 (4.3499); 281 (4.4066); 272 (4.3845); 253 (4.2782); 249 (4.2825); 242 (4.3021); 224 (4.9729)	90

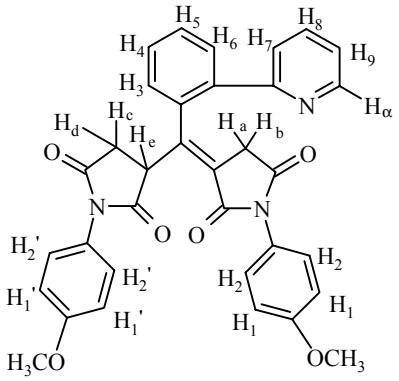
TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized*



Compound	Chemical shifts, δ, ppm						
	H_α pyridine, 1H, d	H_γ pyridine, 1H, m	H_{arom}	H_e (1H)		H_a, H_b, H_c, H_d (4H, m)	Other signals
				enol form (br signal)	keto form (m)		
4a	8.59	7.86	7.15-7.75 (16H)	5.98	4.26	2.85-3.25	
4b	8.58	7.78	7.08-7.32, 7.47-7.67 (14H)	~6	4.24	2.70-3.24	2.37 (6H, s, 2$\underline{H}_3$C–C_{arom})
4c	8.58	7.81	6.92-6.99, 7.10-7.30, 7.48-7.64 (14H)	~6	4.24	2.69-3.16	3.82 (6H, s, 2$\underline{H}_3$C–O–C_{arom})
4d	8.46	8.16	7.17-7.22, 7.35-7.63, 7.68-7.77 (14H)	~5.8	4.20	2.64-3.08	
4e	8.57	7.87	7.03-7.71 (6H)	~5.5	4.01	2.77-3.06	10.98 (1H, s, NH), 11.26 (1H, s, N$\underline{H}$)
4f	8.42	7.71	7.08-7.56 (16H)	~5.95	4.13	2.58-2.96	4.51-4.73 (4H, m, 2NC$\underline{H}_2$Ph)
4g	8.76	8.10	7.24-8.03 (24H)	~6.2	4.40	2.70-3.10	

* According to the integrated intensity data for the H_e signals the content of enol form (see Scheme 2) was 30-80% for compounds **4a,b,d,f**.

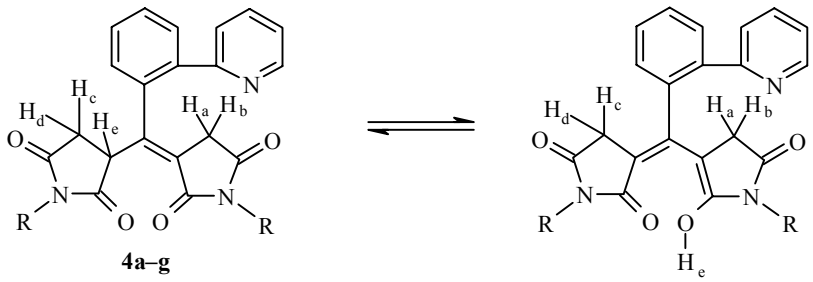
TABLE 3. ^{1}H NMR Spectrum of Compound **4c**



Proton	δ, ppm (*J*, Hz)	
	Atropoisomer **A**	Atropoisomer **B**
H_a	2.73 (d, 21.9)	2.785 (d, 21.7)
H_b	3.06 (d, 21.9)	3.01 (d, 21.7)
H_c (*cis* to H_e)	2.95 (dd, 6.4; 18.8)	3.14 (d, 8.9)
H_d	3.16 (dd, 9.2; 18.8)	3.14 (d, 8.9)
H_e*	4.17-4.29 (m)	3.8-3.92 (m)
OCH_3	3.818 (s)	3.818 (s)
$H_1 + H_1'$	6.953 (d, 8.97)	6.945 (d, 9.18)
$H_2 + H_2'$	7.198 (d, 8.98); 7.224 (d, 8.98)	7.163 (d, 9.02)
H_3; H_4, H_5; H_6;	7.41-7.72 (m)	7.41-7.72 (m)
H_7; H_8; H_9	7.825 (td, 7.66; 1.8)	7.81 (td, 7.66; 1.8)
$H_{\alpha\text{-pyridine}}$	8.593 (dd, 4.8; 0.8.)	8.583 (dd, 4.77; 0.9)

* Signal intensity allowing for the broadened signal at 6 ppm.

Scheme 2

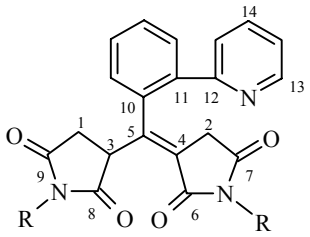


4a–g

To check on the existence of the enol form the ^{1}H NMR spectra of these substances were investigated in $CDCl_3$ in the presence of D_2O. There were no visible changes in the spectra taken immediately after preparing the solutions. Only after keeping the solutions for 6 h did the H_e signal disappear, which is linked with the slow process of enolization.

The enolization is also confirmed by the fact that the signals of the having lost a proton C_3 atom disappeared completely from the ^{13}C NMR spectrum of compound **4c** in $CDCl_3$ with added D_2O after storage for 1 day (Table 4).

TABLE 4. ^{13}C NMR Spectra of Compounds **4a-c** and **4f**



Atoms C	δ, ppm			
	4a	**4b**	**4c**	**4f**
$\underline{C}H_{2\ succinimides}$ (C_1, C_2)	34.84, 35.08, 35.18, 37.59	34.82, 35.07, 35.17, 37.62	35.02, 35.12, 37.59	34.22, 34.92, 34.99, 37.18
$\underline{C}H_e$ (C_3)	44.26, 48.11	44.19, 48.13	44.31, 48.06	43.44
C_4	124.70	124.80	125.22	124.61
C_5	150.52	150.33	150.32	148.64
$\underline{C}$=O (C_6, C_7, C_8, C_9)	157.33, 157.79, 157.84, 167.82, 172.28, 172.45, 175.23, 175.78	157.36, 157.82, 167.91, 169.00, 172,48, 172.65, 175.87, 176.01	157.82, 168.03, 169.00, 172.79, 172.63, 176.18	157.34, 157.72, 168.25, 169.18, 172.98, 173.16, 176.20, 176.48,
C_{10}	137.72	137.76	137.73	137.07
C_{11}	138.53	138.71	139.00	138.31
$C_{2\ pyridine}$ (C_{12})	148.89	148.55	148.91	147.78
C_4 и $C_{6\ pyridine}$	149.04	148.91	149.06	148.64
(C_{14} и C_{13})	149.04	149.067	149.06	149.02
All remaining aromatic C atoms, including substituent R	122.08, 122.35, 122.63, 122.74, 122.84, 126.34, 126.53, 127.09, 127.56, 128.57, 128.96, 129.00, 129.11, 129.16, 129.56, 129.72, 130.15, 131.58, 132.62	122.38, 122.73, 122.84, 126.13, 126.32, 126.35, 126.91, 127.60, 128.90, 129.07, 129.52, 129.58, 129.65, 129.69, 129.82, 130.00, 130.17	114.28, 114.33, 114.50, 122.37, 122.72, 122.84, 124.20, 124.29, 124.74, 127.57, 127.75, 128.31, 128.91, 129.52, 129.71, 130.17	122.36, 122.52, 122.71, 127.13, 127.57, 127.71, 127.86, 127.92, 128.21, 128.47, 128.61, 128.81, 128.91, 129.00, 129.23, 129.35, 129.54, 129.61, 129.85
Other C atoms		21.27 $\underline{C}H_3$–C_{aryl}	55.50 $\underline{C}H_3O$–C_{aryl}	41.20, 41.79, 42.17, 42.76 N–$\underline{C}H_2$Ph

Transfer of the H_e proton on going from the ketone form to the enol is regarded as a usual enolization or as a 1,5-sigmatropic shift, which points to the existence of not one but two enolic forms, i.e. the double bond emerges alternately in both succinimide rings. However such an assertion requires additional confirmation.

EXPERIMENTAL

The ^{13}C NMR spectra were taken on a Bruker AC 250 spectrometer (62.986 MHz) in $CDCl_3$. The ^1H NMR spectra were recorded on a Bruker WP 100 instrument (100 MHz) (Table 2), but for compound **4c** on a Bruker DRX 500 spectrometer (500 MHz) (Table 3) in $CDCl_3$ (relative to TMS). The UV spectra were recorded on a Specord UV-vis instrument in isopropanol. The IR spectra were taken on a Pye Unicam SP3-300 instrument in KBr tablets. Melting points were determined on a Thiele instrument. The purity of products was checked by TLC (Silufol UV 254, chloroform–isopropanol, 10:1).

Pyrido[2,1-*a*]isoindole **1** was obtained by the procedure of [10].

General Procedure for Obtaining Adducts (4a-g). A mixture of compound **1** (2 mmol) and the appropriate maleimide (4 mmol) was refluxed in isopropanol (30-50 ml). The content of the reaction mixture was checked by TLC. After disappearance of the dienophile from the mixture, the solution was cooled. The adduct, which precipitated as a solid, was filtered off, and recrystallized from isopropanol (for compounds **4a-e**) or chloroform (for compounds **4f,g**).

REFERENCES

1. Z. V. Voitenko, V. P. Samoilenko, V. A. Kovtunenko, V. Yu. Gurkevich, A. K. Tyltin, V. M. Shcherbakov, and O. V. Shishkin, *Khim. Geterotsikl. Soedin.*, 669 (1999).
2. V. A. Kovtunenko, Z. V. Voitenko, V. L. Sheptun, L. I. Savranskii, A. K. Tyltin, and F. S. Babichev, *Ukr. Khim. Zh.*, **51**, 976 (1985).
3. V. A. Kovtunenko, Z. V. Voitenko, L. I. Savranskii, A. K. Tyltin, and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, 216 (1988).
4. H. Hennige, R. Kreher, and J. Uhrig, *J. Chem. Soc., Chem. Commun.*, 842 (1982).
5. S. Kajigaeshi, S. Mori, S. Fujisaki, and S. Kamenasa, *Bull. Chem. Soc. Japan*, **58**, 3547 (1985).
6. Z. V. Voitenko, O. O. Shkarov, O. O. Taranenko, and F. S. Babichev, *Nitrogen-containing Heterocycles, Abstracts of the Ukrainian Conference*, Kharkov (1997), p. 56.
7. V. A. Kovtunenko and F. S. Babichev, *Chemistry of Isoindole* [in Russian], Naukova Dumka, Kiev (1983).
8. V. M. Potapov, *Stereochemistry* [in Russian], Khimiya, Moscow (1988).
9. Z. V. Voitenko and O. I. Ostrovskaya, *Abstracts of the XVIII Ukrainian Conference on Organic Chemistry*, Dnepropetrovsk (1988), p. 228.
10. A. Fozard and C. Bradsher, *J. Org. Chem.*, **32**, 2966 (1967).