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CYCLOADDITION IN CONDENSED ISOINDOLES. 3*. SYNTHESIS OF NOVEL TRICYCLIC DERIVATIVES OF THE 7-AZABENZONORBORNENE SYSTEM

Z. V. Voitenko and V. P. Samoilenko

We have studied the reaction of 6-methyl-5,6-dihydroisoindolo[2,1-a]quinazolin-5-one with maleinimide derivatives for a 1:2 reagent ratio. We have shown that the reaction products are tricyclic derivatives of the 7-azabenzonorbornene system, and specifically 11-(2,5-dioxo-1-R-tetrahydro-1H-3-pyrrolyl)-2-methyl-20-R-2,10,20-triazahexacyclo[9.6.5.0^{1,10}.0^{4,9}.0^{12,17}.0^{18,22}]docosa-4(9),5,7,12(17),-13,15-hexaene-3,19,21-triones. We discuss a hypothesis for a probable reaction mechanism.

Keywords: 7-azabenzonorbornenes, condensed isoindoles, cycloaddition.

Continuing the systematic study of the reaction of 6-methyl-5,6-dihydroisoindolo[2,1-*a*]quinazolin-5-one (**1**) with maleinimide derivatives **2a-g** [2], we began studying their reaction with a 1:2 ratio of reagents. From literature sources, we know that in some cases when 1,2-disubstituted isoindoles react with maleinimide derivatives, 1:2 adducts may form [3]. Their formation is interpreted as an initial Michael's addition of one molecule of maleinimide with subsequent cycloaddition of a second dienophile molecule to the 1,2,3-trisubstituted isoindole formed, but now according to a Diels–Alder reaction. However, earlier in our laboratory it was shown that reaction of pyrido[2,1-*a*]isoindole (14 π-electron system) with maleinimide derivatives for a 1:2 reagent ratio leads to nontraditionally rearranged adducts: 3-{2,5-dioxo-1-R-tetrahydro-1H-3-pyrrolylidene[2-(2-pyridyl)phenyl]methyl}-1-R-2,5,-pyrrolidinediones [1]. We carried out the reaction of isoindole **1** with maleinimide derivatives analogously. When the reagents were heated or refluxed in different solvents ($CHCl_3$, C_2H_5OH, *i*-C_3H_7OH, dioxane, $C_6H_5CH_3$), we unexpectedly obtained 11-(2,5-dioxo-1-R-tetrahydro-1H-3-pyrrolyl)-2-methyl-20-R-2,10,20-triazahexacyclo[9.6.5.0^{1,10}.0^{4,9}.0^{12,17}.0^{18,22}]docosa-4(9),5,7,-12(17),13,15-hexaene-3,19,21-triones of general formula **3** (Scheme 1).

The purity of the products was demonstrated by TLC. The structure of compounds **3a-g** was established on the basis of elemental analysis and spectral data.

Elemental analysis for N confirms that the products obtained are 1:2 adducts (Table 1). For adduct **3a**, we obtained a mass spectrum corresponding to a 1:2 adduct, which clearly proves the quantitative composition of the compounds obtained.

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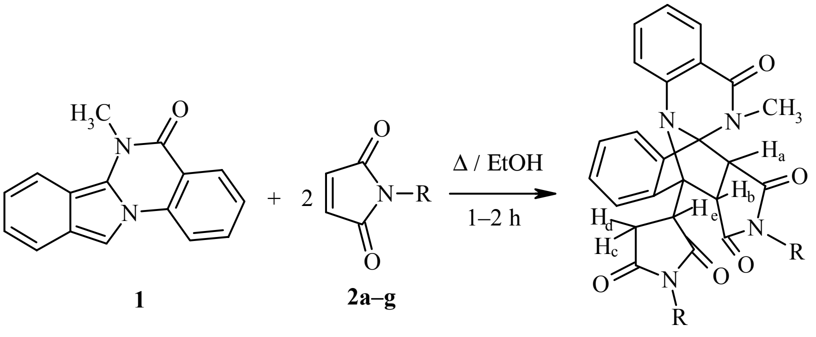
* For Communication 2, see [1].

Kiev Taras Shevchenko National University, Kiev 01033; e-mail: olya@serv.biph.kiev.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 218-226, February, 2002. Original article submitted November 14, 2000.

Scheme 1



2, 3, a R = H; **b** R = CH_2Ph; **c** R = Ph; **d** R = 2-Npht; **e** R = $C_6H_4CH_3$-*p;*
f R = 2,5-dimethylphenyl; **g** R = $C_6H_4NO_2$-*p*

In the IR spectra of these products, there are stretching vibration bands for the C=O groups and skeletal vibration bands for the aromatic C=C bonds (Table 1). The UV spectra of compounds **3b,d,g** are consistent with the proposed structure, since there is an absorption band typical for aromatic conjugated chromophores, and there is no isoindole long-wavelength absorption. The signals in the ^{1}H NMR spectra also correspond to the proposed structure. So the ^{1}H NMR spectra of compounds **3a-g** made it possible to identify all the aliphatic and some of the aromatic protons; for example, a signal for the 5-H aromatic proton is observed in the 7.75-8.38 ppm region and is downfield from the other protons at 0.2-0.5 ppm. Such a large chemical shift for 5-H can be explained by the deshielding effect of the carbonyl group of the quinazolone moiety. The Michael's moiety (2,5-dioxo-1-R-tetrahydro-1H-3-pyrrolyl) in the structures of **3a-g** gives three doublets of doublets, which also was expected based on theoretical reasoning. The geminal spin–spin coupling constants (17-18 Hz) in this moiety coincide with the typical spin–spin coupling constants for such groups [1]. The two bridge protons H_a and H_b appear in the ^{1}H NMR spectrum as two doublets with spin–spin coupling constant 7.5-7.8 Hz. Such a value is typical for bridge protons of a 7-azabenzonorbornene system, and matches that calculated from the Karplus formula. Additional proof of the structure for the compounds obtained comes from the COSY spectrum taken for compound **3b** (Fig. 1). From this spectrum, we clearly see the interaction of the bridge protons H_a and H_b with each other, and also of the protons of the Michael's moiety H_c, H_d, and H_e respectively.

However, based only on the ^{1}H spectra, we cannot exclude the possibility of formation of *exo* Diels–Alder adducts **4** and also nontraditional rearranged adducts of general formula **5**, as described for the reaction in the case of pyrido[2,1-*a*]isoindole with maleinimide derivatives for a 1:2 reagent ratio [1].

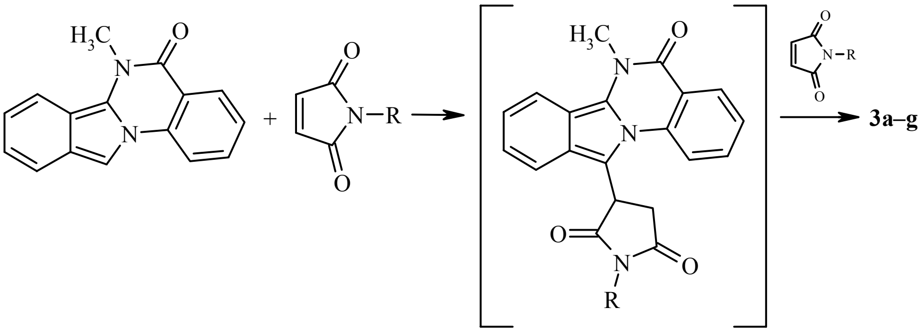


TABLE 1. Characteristics of Synthesized Compounds **3a-g**

Compound	R	Empirical formula	Found, % Calculated, %	mp, °C	R_f	IR spectrum, $\nu_{C=O}$, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	Yield, %
3a	H	$C_{24}H_{18}N_4O_5$	12.86 12.66	205-207	0.20	1775, 1705, 1640, 1605		59
3b	CH_2Ph	$C_{38}H_{30}N_4O_5$	9.21 9.00	170-172	0.75	1775, 1700, 1650, 1600	312.0 (3.24)	66
3c	Ph	$C_{36}H_{26}N_4O_5$	9.22 9.42	160-162	0.72	1780, 1710, 1650, 1590		60
3d*	2-Npht	$C_{44}H_{30}N_4O_5$	8.21 8.06	168-169	0.73	1775, 1705, 1650, 1600	222.6 (4.42), 271.1 (3.45), 281.2 (3.48), 292.0 (3.38)	78
3e	$C_6H_4CH_3$-*p*	$C_{38}H_{30}N_4O_5$	9.07 9.00	164-166	0.76	1775, 1700, 1650, 1600		74
3f	2,5- Dimethylphenyl	$C_{40}H_{34}N_4O_5$	8.88 8.61	214-216	0.75	1775, 1700, 1640, 1595		69
3g	$C_6H_4NO_2$-*p*	$C_{36}H_{24}N_6O_9$	12.58 12.28	204-206	0.70	1780, 1715, 1655, 1600	309.7 (3.34)	61

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* The UV spectrum was recorded in ethanol.

TABLE 2. ^{1}H NMR Spectra of Compounds **3a-g**

Compound	Chemical shifts, δ, ppm										Spin-spin coupling constants (J), Hz				
	N–H_3 3H, s	H_a 1H, d	H_b 1H, d	H_c 1H, dd	H_d 1H, dd	H_e 1H, dd	H_{arom}			Other protons	^3J H_a,H_b	^3J H_c,H_e; ^3J H_d,H_e	^2J H_c,H_d	^3J 15-H, 16-H	^3J 5-H, 6-H
							5-H 1H, d	16-H 1H, d	6-, 7-, 8-, 13-, 14-, 15-H, R						
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
3a	3.61	3.77	3.16	3.06	2.58	4.72	7.75	7.64	6.93 (1H, t, ^3J = 7.5); 7.00 (1H, d, ^3J = 8.5); 7.10-7.50 (4H, m)	11.52 (1H, s, NH); 11.84 (1H, s, NH);	7.5	6.9; 10.1	18.1	7.3	
3b	3.67	3.94	3.28	3.06	2.31	4.86	7.77	7.66	6.94 (1H, t, ^3J = 7.5); 6.97 (1H, d, ^3J = 8.3); 7.10-7.50 (14H, m)	4.59 (1H, d, ^2J = 15.2, C$\underline{H_2}$^{a}Ph); 4.66 (1H, d, $\underline{H_2}$^{a}Ph); 4.74 (1H, d, ^2J = 15.1, C$\underline{H_2}$^{b}Ph); 4.81 (1H, d, C$\underline{H_2}$^{b}Ph);	7.6	6.6; 9.7	17.9	7.2	
3c*	4.17	4.44	4.12	3.89	3.55	5.36	8.38	8.15	6.97 (1H, t, ^3J = 7.5); 7.13 (1H, t, ^3J = 8.3); 7.20-7.65 (12H, m); 7.88 (2H, d, ^3J = 7.1)	—	7.7	6.7; 10.0	18.7	7.4	7.6

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
3d	3.69	4.18	3.63	3.47	2.80	5.43	7.94	7.86	7.00-7.80 (16H, m); 8.00-8.20 (4H, m)	—	7.5	7.0; 10.6	17.6	7.6	7.7
3e	3.66	4.03	3.37	3.39	2.77	5.00	7.79	7.72	6.97 (1H, t, $^3J = 8.5$); 7.08 (1H, d, $^3J = 8.9$); 7.11 (2H, d, $^3J = 8.3$); 7.19-7.47 (10H, m)	2.34 (3H, s, CH_3C_{arom}); 2.37 (3H, s, CH_3C_{arom})	7.7	7.5; 10.5	17.5	7.3	7.8
3f	3.66	4.00	3.47	3.38	2.72	5.13	7.79	7.70	6.81-7.46 (12H, m)	2.23 (3H, s, CH_3C_{arom}); 2.25 (3H, s, CH_3C_{arom}); 2.27 (3H, s, CH_3C_{arom}); 2.31 (3H, s, CH_3C_{arom})	7.6	7.1; 9.4	16.8	7.3	7.9
3g	3.69	4.16	3.46	3.51	2.91	5.10	7.80	7.75	6.99 (1H, t, $^3J = 7.4$); 7.03 (1H, d, $^3J = 7.5$); 7.20-7.74 (10H, m); 8.37 (2H, d, $^3J = 9.0$); 8.46 (2H, d, $^3J = 8.9$)	—	7.8	7.0; 10.0	18.3	8.0	7.9

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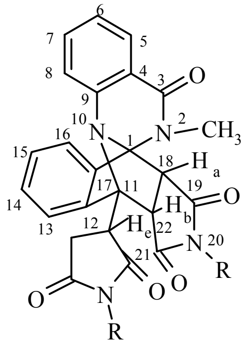
* The spectrum was recorded in pyridine-d$_5$.

TABLE 3. ^{13}C NMR Spectral Data for Synthesized Compounds **3a,b,g**

Compound	Chemical shifts, δ, ppm								
	N–CH_3	$CH_{2\ pyrrole}$	$CH_{pyrrole}$	CH_{bridge}	C_{aliph}	CH_{arom}	C_{arom}	C=O	Other C atoms (NCH_2)
3a	32.34	34.97	43.75	49.56; 50.02	73.13; 85.63	115.94; 120.65; 121.70; 122.32; 127.56; 128.02; 128.49; 133.48	119.14; 143.25; 143.99; 145.33	160.98; 174.40; 176.34; 176.55; 177.73	—
3b	32.43	33.35	42.35	48.43; 48.87	73.19; 85.95	115.87; 120.87; 121.85; 122.28; 127.32; 127.44; 127.53; 127.60; 127.79; 128.10; 128.24; 128.34; 128.53; 133.43;	119.11; 135.24; 135.98; 143.09; 143.69; 145.11	161.00; 172.88; 174.80; 174.88; 176.30	41.75 NCH_2); 41.93 (NCH_2)
3g	32.54	33.93	42.81	48.73; 49.42	73.47; 86.34	115.87; 121.29; 122.12; 122.25; 124.35; 124.48; 127.78; 127.97; 128.13; 128.39; 128.70; 133.62	119.41; 136.89; 137.86; 143.07; 143.85; 144.90; 146.79; 147.12	161.10; 171.82; 173.53; 174.32; 175.02	—



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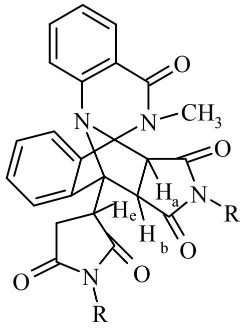

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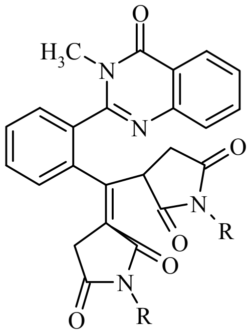

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In order to choose between structures **3, 4,** or **5**, we studied the ^{13}C NMR spectra. Application of a procedure which makes it possible to separate signals for the carbon atoms of the CH_2 group and quaternary carbon atoms from signals of the methyl and methine groups (Table 3) unambiguously excludes formation of compounds with structure **5** in the reaction described. Thus in ^{13}C NMR spectra of the synthesized compounds, there are three signals from aliphatic CH groups, one signal from the CH_3 group, and one signal from the aliphatic CH_2 group, which corresponds to structure **3** or structure **4** but not structure **5**. The presence of two signals for quaternary aliphatic carbons conclusively eliminates structure **5**, since there are no quaternary aliphatic carbon atoms in it.

Formation of specifically the *endo* Diels–Alder adduct **3** rather than the *exo* Diels–Alder adduct **4** is indirectly confirmed by the significant difference (0.5-0.7 ppm) between the chemical shifts of the bridge protons H_a and H_b. In the case of the *endo* adduct, the protons H_a and H_b should be found in nonequivalent environments due to the deshielding effect of the quinazolone moiety on the nearby H_a proton. In the case of the *exo* adduct, the H_a and H_b protons are found in approximately identical environments and the difference between their chemical shifts should be fairly small.

The reaction can be explained as follows. We hypothesize that the reaction begins with Michael's addition of one molecule of maleinimide, and that the intermediate formed adds a second maleinimide molecule to form the *endo* Diels–Alder adduct.

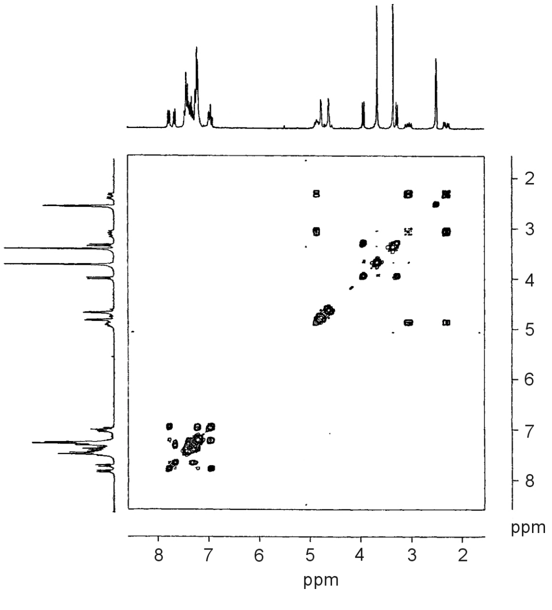


Fig. 1. COSY ^{1}H NMR spectrum of adduct **3b**.

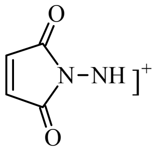
Formation of such products as a result of addition of maleinimide derivatives to the 6-methyl-5,6-dihydroisoindolo[2,1-*a*]quinazolin-5-one system is unexpected, since earlier it was hypothesized that the intermediate Diels–Alder adduct is a strained tricyclic system and should rapidly rearrange to a nontraditional rearrangement adduct [1]. However, as we see, such three-dimensional structures are quite stable for the 6-methyl-5,6-dihydroisoindolo[2,1-*a*]quinazolin-5-one system.

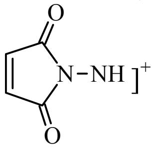
Thus we have shown that upon heating and with a 1:2 reagent ratio, in the case of 6-methyl-5,6-dihydroisoindolo[2,1-*a*]quinazolin-5-one, derivatives of the 7-azabenzonorbornene system are formed that are distinguished from the described products of the same reaction for pyrido[2,1-*a*]isoindole. We should note that synthesis of such a novel heterocyclic system is the first example of isolation of stable representatives of tricyclic 7-azabenzonorbornenes.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker CPX-250 (250 MHz) in DMSO-d$_6$ relative to TMS. The ^{13}C NMR spectra of compounds **3a,b,g** were recorded in DMSO-d$_6$ on a Bruker-250 (62.9 MHz). The IR spectra were recorded on a Pye Unicam SP3-300 spectrometer in KBr pellets. The UV spectra were measured on a Perkin–Elmer Lambda-19 for solutions in 1,4-dioxane. The melting points were determined on a Boetius (GDR) hot stage. The mass spectra were recorded on a Nermag R 10 spectrometer. The course of the reaction and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in a 10:1 chloroform–methanol system. The characteristics of the compounds obtained are presented in Tables 1-3.

General Procedure for Obtaining Compounds 3a-g. A mixture of the corresponding maleinimide **2** (6 mmol) and 6-methyl-5,6-dihydroisoindolo[2,1-*a*]quinazolin-5-one (3 mmol) were heated under reflux in EtOH (15-30 ml) for 1-2 h. The reaction mixture was cooled down, and the precipitate of product **3** was filtered off and recrystallized from dioxane. A white material was obtained.

Mass spectrum of compound **3a** (electrospray, 5 μl/min, CH$_3$CN), *m/z* (*I*, %): [2MH]$^+$ 885 (8), [MH]$^+$ 443 (72), [M - 

]$^+$ 346 (100), [M - 2 

]$^+$ 248 (19).

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