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DIENE SYNTHESIS WITH 5-CHLORO-1-ALKYL-2-PYRIDONES

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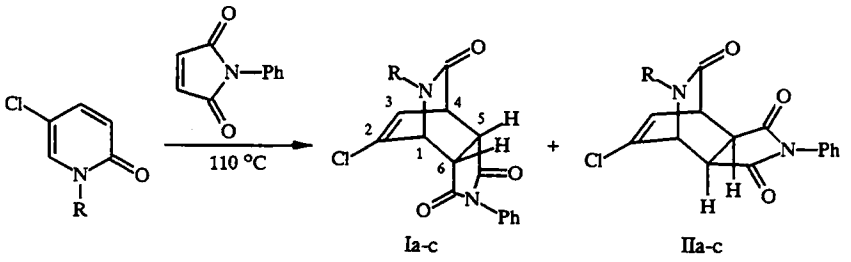
For the first time, we describe the diene synthesis of 5-chloro-1-alkyl-2-pyridones with N-phenylmaleic imide and have shown that the reaction proceeds nonstereoselectively with formation of a mixture of [4+2]cycloadducts with an endo *and* exo *configuration. We have obtained 1,4-cycloadducts with 4-phenyl-1,2,4-triazoline-3,5-dione.*

Reactions of diene synthesis with 2-pyridones as the diene component allow us to obtain bicyclic systems with an endazocarbonyl bridge (derivatives of azabicyclo[2.2.2]octene). Data quite interesting from a theoretical standpoint were obtained when studying the stereochemistry of diene synthesis with these six-membered heterocycles [1].

In this work, for the first time we have carried out a diene synthesis for 5-chloro-1-alkyl-2-pyridones with N-phenylmaleic imide and 4-phenyl-1,2,4-triazoline-3,5-dione. We might expect that chloro-substituted pyridones containing an electron-acceptor substituent in the molecule should enter into a diene synthesis reaction with more difficulty than pyridones not containing a halogen, with which the Diels–Alder reaction has been previously accomplished at 140°C [2]. Therefore initially the reaction of 5-chloro-1-methylpyridone with N-phenylmaleic imide was done at 180°C (heating in decalin). But since considerable tar formation occurred, subsequent experiments were performed at lower temperatures, and the length of time the reagents were in contact was varied. The best yield of cycloadducts (89%) was obtained when the reagents were boiled in toluene solution for 40 h. Achievement of such a yield in benzene required a significantly longer heating time (90 h). The optimal ratio of starting reagents was 1:1.5 pyridone–N-phenylmaleic imide.



Ia-c IIa-c

I, II a R = Me, b R = Et, c R = Bu

In all the examples, we obtained 1,4-cycloadducts as a mixture of two stereoisomers, which were separated by chromatography on aluminum oxide and fractional crystallization.

The composition of adducts Ia-c and IIa-c was established based on elemental analysis and mass spectra, while the configuration was established with the help of PMR spectra and mass spectrometry.

According to the rule discovered earlier for alkyl-substituted pyridones [3, 4], adducts for which the spin–spin coupling constant of the bridging protons with adjacent protons (J_{16} and J_{45}) is greater than 3.5 Hz are assigned an *endo* configuration, and those for which these constants prove to be less than 3.5 Hz are assigned the *exo* configuration.

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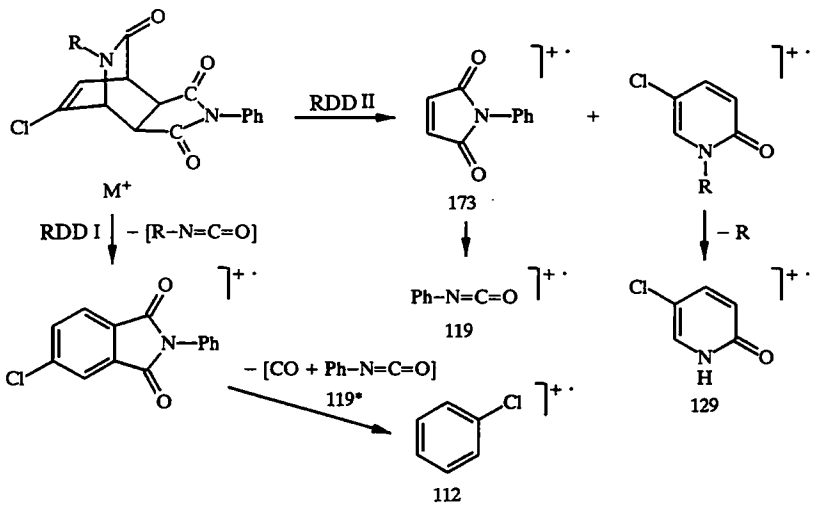
TABLE 1. Characteristics of Synthesized Compounds I-III

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	R_f	Yield, %
		C	H	Cl	N			
Ia	$C_{16}H_{13}ClN_2O_3$	60.78 60,66	4.27 4,11	11.30 11,21	8.90 8,85	208...210	0.33	70
IIa	$C_{16}H_{13}ClN_2O_3$	60.45 60,66	4.07 4,11	11.08 11,21	8.60 8,85	260...261	0,65	19
Ib	$C_{17}H_{15}ClN_2O_3$	61.79 61,72	4.59 4,54	10.46 10,74	8.30 8,47	165...166	0,25	62
IIb	$C_{17}H_{15}ClN_2O_3$	61.68 61,72	4.50 4,54	10.51 10,74	8.40 8,47	243...244	0,58	13
Ic	$C_{19}H_{19}ClN_2O_3$	63.31 63,59	5.58 5,30	10.11 9,90	7.84 7,81	121...122	0,45	57
IIc	$C_{19}H_{19}ClN_2O_3$	63.69 63,59	5.43 5,30	9.76 9,90	7.62 7,81	182...184	0,77	10
IIIa	$C_{14}H_{11}ClN_4O_3$	53.11 52,75	3.73 3,45	11.35 11,14	17.49 17,58	154...156 (decomp.)	—	73
IIIb	$C_{15}H_{13}ClN_4O_3$	54.16 54,13	4.13 3,91	10.51 10,68	17.18 16,85	132...134 (decomp.)	—	74
IIIc	$C_{17}H_{17}ClN_4O_3$	56.62 56,58	4.87 4,72	10.25 9,85	15.71 15,53	98...100 (decomp.)	—	74

Earlier in studying the mass spectra of *endo* and *exo* adducts of alkyl-substituted pyridones [5], the characteristic features of fragmentation of these isomers were determined and it was shown to be possible to establish the configuration of adducts when both stereoisomers are present. Decomposition of 1,4-cycloadducts under electron impact occurs in two directions: with cleavage of the endazocarbonyl bridge (RDD I) and retrodiene decomposition with formation of the starting reagents (RDD II).



*Here and in the following, the *m/z* values are given for the ion peaks.

We have established that for the *endo* adduct, the probability of retrodiene decomposition in both directions is greater than for the *exo* adduct, and the stability of the molecular ion is slightly lower.

Investigation of the mass spectra of the stereoisomeric cycloadducts Ib and IIb obtained from 5-chloro-1-ethylpyridone supported the assignment of the configuration of adduct Ib to the *endo* series and assignment of the configuration of adduct IIb to the *exo* series which we made based on the PMR spectra, since for adduct Ib the probability of retrodiene decomposition (RDD I 34%, RDD II 3.1%) is higher than for adduct IIb (RDD I 26.8%, RDD II 1.7%). Furthermore, the stability of the molecular ion of isomer Ib was lower than for isomer IIb (0.7 and 0.8 respectively).

With the goal of determining if the two stereoisomers are obtained as a result of isomerization of the initially formed *endo* adduct or if they are formed as a result of two kinetically independent processes, we carried out pyrolysis of the *endo*

TABLE 2. Spectral Characteristics of Adducts I-III

Compound	PMR spectrum, δ, ppm (J, Hz)	Configuration	Mass spectrum, m/z values (I, %)
Ia	2,94 (3H, s, CH_3); 3,23 - 3,74 (2H, m, 5-H, 6-H); 3,95 (1H, q, 4-H, J_{45} = 3,70); 4,52 (1H, q, 1-H, J_{16} = 4,20); 6,28 (1H, q, 3-H); 6,95 - 7,55 (5H, m, Ph)	*endo*	316 (M^+ 2,6), 262 (6,5), 261 (16), 260 (21,5), 259 (45,6), 145 (4), 143 (11), 129 (5), 119 (100), 114 (7), 112 (27)
IIa	2,83 (3H, s, CH_3); 3.20 - 3,72 (2H, m, 5-H, 6-H); 4,02 (1H, q, 4-H, J_{45} = 3,30); 4,51 (1H, q, 1-H, J_{16} = 3,0); 6,31 (1H, q, 3-H); 6,93 - 7,53 (5H, m, Ph)	*exo*	316 (M^+ 1,9), 262 (3), 261 (8,2), 260 (10,2), 259 (22,5), 145 (2,5), 143 (5), 129 (2,3), 119 (100), 114 (4), 112 (15)
Ib	1,08 (3H, t, CH_3); 2,80 - 3,88 (4H, m, CH_2, 5-H, 6-H); 3,98 (1H, q, 4-H, J_{45} = 3,70); 4,59 (1H, q, 1-H, J_{16} = 4,25); 6,32 (1H, q, 3-H); 6,95 - 7,55 (5H, m, Ph)	*endo*	330 (M^+ 1,9), 262 (5), 261 (33), 260 (15), 259 (100), 159 (3), 157 (9), 131 (3), 129 (9), 119 (93), 114 (18), 112 (60)
IIb	1,00 (3H, t, CH_3); 2,72 - 3,88 (4H, m, CH_2, 5-H, 6-H); 3,97 (1H, q, 4-H, J_{45} = 3,30); 4,56 (1H, q, 1-H, J_{16} = 3,00); 6,32 (1H, q, 3-H); 6,95 - 7,53 (5H, m, Ph)	*exo*	330 (M^+ 1,5), 262 (2,4), 261 (15), 260 (7,3), 259 (45,4), 159 (1), 157 (3), 119 (100), 114 (8), 112 (25)
Ic	0,65 - 1,62 (5H, m, CH_2CH_3); 3,08-3,70 (6H, m, CH_2CH_2, 5-H, 6-H); 3,87 (1H, q, 4-H, J_{45} = 3,70); 4,54 (1H, q, 1-H, J_{16} = 4,20); 6,29 (1H, q, 3-H); 6,95 - 7,52 (5H, m, Ph)	*endo*	358 (M^+ 1,4), 262 (2), 261 (13,8), 260 (6,2), 259 (38,3), 143 (2,9), 131 (0,8), 129 (2,3), 119 (100), 114 (6,2), 112 (19,4)
IIc	0,57-1,51 (5H, m, CH_2CH_3); 3,13-3,85 (6H, m, CH_2CH_2, 5-H, 6-H); 3,98 (1H, q, 4-H, J_{45} = 3,20); 4,51 (1H, q, 1-H, J_{16} = 3,00); 6,38 (1H, q, 3-H); 6,88-7,50 (5H, m, Ph)	*exo*	358 (M^+ 1,1), 262 (1), 261 (6), 260 (3,3), 259 (20,1), 143 (1,3), 129 (1,2), 119 (100), 114 (3,3), 112 (9,5)
IIIa	3,05 (3H, s, CH_3); 5,27 (1H, q, 4-H, J_{43} = 6,3); 5,76 (1H, d, 1-H, J_{13} = 2,6); 6,52 (1H, q, 3-H, J_{31} = 2,6, J_{34} = 6,3); 7,31-7,52 (5H, m, Ph)	—	318 (M^+ 0,8), 177 (20,3), 145 (35), 143 (100), 119 (50), 117 (15,5), 115 (47,5), 114 (11), 108 (9,5), 91 (16,4), 80 (92,5)
IIIb	1,13 (3H, t, CH_3); 3,45 (2H, q, CH_2); 5,27 (1H, d, 4-H, J_{43} = 6,5); 5,80 (1H, d, 1-H, J_{13} = 2,7); 6,49 (1H, q, 3-H, J_{31} = 2,7, J_{34} = 6,5); 7,31-7,43 (5H, m, Ph)	—	332 (M^+ 0,7), 177 (21), 159 (30), 157 (100), 119 (49), 117 (13), 129 (45), 128 (9,7), 122 (10), 91 (15), 80 (91,3)
IIIc	0,69-1,76 (7H, m, $CH_2CH_2CH_3$); 3,38 (2H, t, CH_2); 5,22 (1H, d, 4-H, J_{43} = 6,5); 5,75 (1H, d, 1-H, J_{13} = 2,6); 6,45 (1H, q, 3-H, J_{31} = 2,6, J_{34} = 6,5); 7,12-7,51 (50, m, Ph)	—	360 (M^+ 0,75), 177 (20), 187 (29), 185 (100), 119 (50), 117 (10), 157 (30), 156 (5), 150 (9,3), 91 (16), 80 (92)

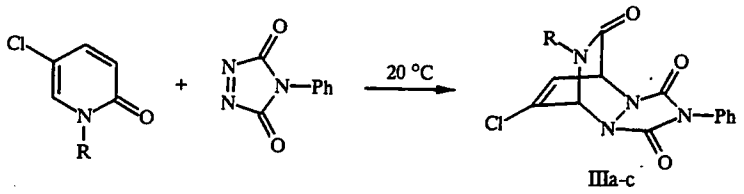
adduct Ia at 174°C (in decane) for 20 h. According to thin-layer chromatography data, *exo* adduct IIb is not formed, which allows us to conclude that the *exo* adduct IIb is obtained directly from chloropyridone and N-phenylmaleic imide.

Thus, the presence of chlorine in the pyridone molecule affects the stereochemistry of the reaction. In contrast to alkylpyridones (without substituents at the ends of the conjugated system of multiple bonds), reactions with chloropyridones proceeded nonstereoselectively with formation of both possible isomers (with predominance of the *endo* adduct). At the same time, we showed that, despite data on the negative effect of electron-acceptor groups on the yield of 1,4-cycloadducts, the chlorine atom results in practically no decrease in the reactivity of halo-substituted pyridones in diene synthesis compared with the corresponding alkylpyridones.

The reaction of 5-chloro-1-alkylpyridones with phenyltriazolinedione occurred at room temperature, but in contrast to alkylpyridones (for which the reaction went to completion in 10-20 min [3]), it required a longer contact time between reagents: 10-15 h (disappearance of the red color of the starting triazolinedione).

The composition and structure of the N-imides of 2-chloro-8-alkyl-5,6,8-triazabicyclo]2.2.2]oct-2-en-7-one-5,6-dicarboxylic acids (IIIa-c) were supported by the results of elemental analysis, PMR, and mass spectra.

In each example, IIIa-c was obtained in good yields (~75%) with respect to a single stereoisomer, which is consistent with literature data on the stereochemistry of diene synthesis of triazolinedione with 1-alkyl-2-pyridones [6-9].



III a R = Me, b R = Et, c R = Bu

EXPERIMENTAL

The PMR spectra were recorded on a Tesla B3 467 spectrometer at a frequency of 60 MHz in $CDCl_3$; internal standard, HMDS. The mass spectra were measured on an LKB-1091 chromatograph–mass spectrometer with temperature of the ionization chamber equal to 120-160°C and ionizing electron energy 70 eV. Chromatography was done on a column with Al_2O_3 (Brockmann activity II).

N-Phenylimides of 2-Chloro-8-alkyl-8-azabicyclo[2.2.2]oct-2-en-one-5,6-dicarboxylic Acid Ia-c, IIa-c. Solutions of chloropyridones and N-phenylmaleic imide (0.006 and 0.009 moles respectively) were boiled in 30 ml toluene for 40 h. The toluene was driven off under vacuum, and the residue was washed several times with ether to remove the starting materials. A reaction product was obtained which according to TLC is a mixture of two compounds. Isomers Ia-c having the *endo* configuration according to PMR spectra were isolated by recrystallization from ethylacetate.

The solution remaining after recrystallization was evaporated and the residue was chromatographed on a column with Al_2O_3 in a 3:2 benzene–ethylacetate system. The *exo* isomers of IIa-c were obtained. The purity of the adducts obtained was monitored by TLC on Al_2O_3 (benzene–ethylacetate, 3:2).

N-Phenylamides of 2-Chloro-8-alkyl-5,6,8-triazabicyclo[2.2.2]oct-2-en-7-one-5,6-dicarboxylic Acid IIIa-c. Ether solutions (100 ml) of equimolar amounts of chloropyridones and freshly distilled phenyltriazolinedione (0.003 moles each) were stirred at room temperature for 10 h. The precipitate was filtered off, washed with ether and then with acetone. Adducts IIIa-c were isolated by recrystallization from benzene.

The constants, yields, and elemental analysis data are presented in Table 1. The PMR spectra are presented in Table 2.

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