DIENE SYNTHESIS WITH 2-PYRONES AND 2-PYRIDONES.

31.* STEREOCHEMISTRY OF THE SUCCESSIVE ADDITION OF TWO DIFFERENT DIENOPHILES TO 2-PYRONES

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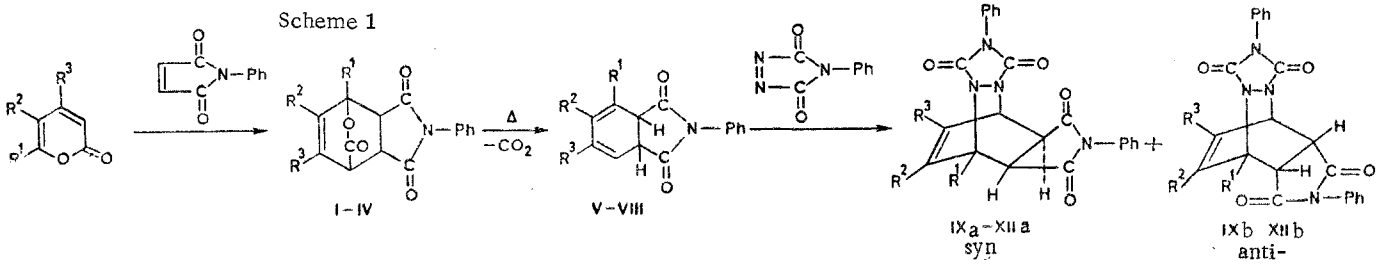
The stereochemistry of the successive addition of two different dienophiles, viz., N-phenylmaleinimide and 4-phenyl-1,2,4-triazoline-3,5-dione, to 2-pyrones was studied. The configurations of the mixed adducts (bisimides) obtained were established by PMR and mass spectrometry. It is shown that in all cases the reactions proceed with the formation of mixtures of syn and anti isomers, the ratios of which depend on the positions of the methyl groups in the starting 2-pyrones.

Double diene synthesis with 2-pyrones, which consists in the addition of two molecules of the dienophile and splitting out of a molecule of CO_2, is widely used for the preparation of bisadducts, viz., compounds of the bicyclo[2.2.2]octene series [2, 3]. However, the stereochemistry of these reactions has not yet been investigated.

In the present research for the first time we studied the configurations of mixed adducts of 2-pyrones with N-phenylmaleinimide (PMI) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTD). In order to ascertain the effect of the structures of the starting dienes on the stereochemistry of the reactions, we selected 6-methyl-, 5,6-dimethyl-, 4-methyl-, and unsubstituted 2-pyrones.

Since mixed bisadducts cannot be synthesized by the direct reaction of 2-pyrones with two different dienophiles, we obtained them in three successive steps. We initially synthesized monoadducts of 2-pyrones with PMI (I-IV) [4, 5], which were then converted to 1,3-cyclohexadienes V-VIII (1,2-dihydrophthalic acid N-phenylimides) by thermal splitting out of CO_2 [3]. The reaction of the resulting compounds with PTD led to the formation of mixed adducts IXa,b and XIa,b from methyl-substituted 2-pyrones, viz., 1-methyl-, 1,6-dimethyl-, and 5-methyl-7,8-diazabicyclo[2.2.2]oct-5-ene-2,3,7,8-tetracarboxylic acid bis-N-phenylimides (XIIa, b from the unsubstituted 2-pyrone.

Scheme 1



I, V, IX a-b $R^1=CH_3, R^2=R^3=H$; II, VI, X a-b $R^1=R^2=CH_3, R^3=H$; III, VII, XI a-b $R^1=R^2=H, R^3=CH_3$; IV, VIII, XII a-b $R^1=R^2=R^3=H$

*See [1] for communication 30.

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TABLE 1. Bis-N-phenylimides IXa,b-XIIIa,b

Compound	mp, °C	m/z values (relative intensities, %)[a]	syn/anti ratio	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
IXa	231—232[b]	414 (10), 242 (16), 241 (100), 238 (2), 237 (4), 119 (25), 95 (6), 94 (86), 93 (5), 92 (38), 91 (35)	1 : 1,5	66,9	4,7	13,6	$C_{23}H_{18}N_4O_4$	66,7	4,4	13,5	40
IXb	257—258[c]	414 (3), 242 (16), 241 (100), 239 (3), 120 (4), 119 (25), 94 (65), 93 (6), 92 (51), 91 (30), 65 (5)		66,6	4,8	13,8	$C_{23}H_{18}N_4O_4$	66,7	4,4	13,5	60
Xa	253,5—254[d]	428 (1), 256 (8), 255 (46), 251 (9), 119 (21), 108 (100), 106 (55), 105 (27), 91 (46), 79 (12), 77 (17)	1 : 1	67,4	5,3	13,1	$C_{24}H_{20}N_4O_4$	67,3	4,7	13,1	52
Xb	243—243,5[e]	428 (2), 256 (12), 255 (78), 119 (15), 109 (7), 108 (100), 106 (58), 105 (13), 91 (41), 79 (10), 77 (9)		67,0	4,9	13,4	$C_{24}H_{20}N_4O_4$	67,3	4,7	13,1	47
XIa	203—205[b]	414 (5), 242 (7), 241 (50), 120 (3), 119 (21), 95 (7), 94 (100), 92 (25), 91 (24), 77 (4), 65 (7)	4 : 1	66,7	4,3	—	$C_{23}H_{18}N_4O_4$	66,7	4,4	13,5	86
XIb	262—263[b]	414 (10), 242 (13), 241 (75), 119 (26), 95 (7), 94 (100), 93 (7), 92 (60), 91 (34), 77 (4), 65 (8)		66,9	4,3	—	$C_{23}H_{18}N_4O_4$	66,7	4,4	13,5	14
XIIa[f]	239—240[b]	400 (14), 228 (14), 227 (94), 223 (22), 175 (16), 119 (75), 91 (20), 80 (100), 78 (34), 77 (12), 76 (20)	4 : 1	—	—	—	—	—	—	—	81
XIIb[f]	319[c]	400 (8), 228 (12), 227 (75), 120 (8), 119 (81), 105 (7), 92 (6), 91 (17), 80 (100), 78 (40), 77 (9)		—	—	—	—	—	—	—	18
XIIIa	229—230[g]	416 (19), 242 (15), 241 (91), 240 (16), 119 (100), 95 (10), 94 (95), 93 (49), 92 (50), 91 (55), 77 (16)	—	66,4	5,0	13,5	$C_{23}H_{20}N_4O_4$	66,4	4,8	13,5	60
XIIIb	249—250[c]	416 (25), 242 (12), 241 (43), 240 (28), 239 (16), 178 (13), 119 (93), 94 (40), 93 (100), 92 (35), 91 (25)	—	66,5	5,0	13,9	$C_{23}H_{20}N_4O_4$	66,4	4,8	13,5	95

[a]The molecular-ion peaks and the 10 most intense peaks are presented. [b]From benzene. [c]From acetone. [d]From chloroform. [e]From ethyl acetate. [f]Adducts XIIa,b were described in [9]. [g]From ethanol.

The selection of PTD as the second dienophile was due to the fact that endo-exo isomerism is not observed for adducts with this dienophile owing to the planar configuration of the nitrogen atoms [6]. Consequently, the stereochemistry of the reactions of dienes with PTD should be determined by the plane-nonsymmetrical character of cyclohexadienes V-VIII, which is responsible for the possibility of approach of the dienophile from the imide ring side and from the opposite sterically less hindered side (syn-anti isomerism) [7], which leads to the formation of two stereoisomers instead of the three that are possible when carbon dienophiles are used.

In each reaction we obtained two stereoisomers (a, b), which were isolated in individual form by means of column chromatography on silica gel. The constants, yields, and results of elementary analysis of synthesized adducts IXa,b-XIIa,b are presented in Table 1.

TABLE 2. PMR Spectra of the Bis-N-phenylimides

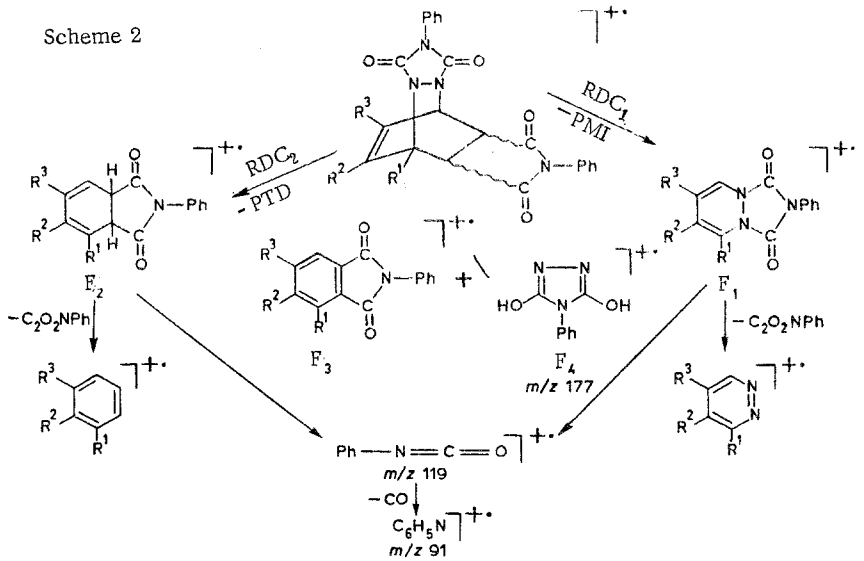
Compound	δ, ppm, No. of protons					Solvent
	CH_3, 5-H—2-H, 6-H—2-H	2-H; 3-H	1-H—4-H	5-H—6-H	aromatic	
IXa	1,95 3H	2,9; 3,3 2H	5,3—5,5 1H	6,1—6,5 2H	6,8—7,2 10H	CF_3COOH
IXb	2,0 3H	3,7; 4,0 2H	5,5—5,8 1H	6,3—6,9 2H	6,8—7,6 10H	CF_3COOH
Xa	1,6; 1,9 3H; 3H	2,7; 3,3 2H	5,1—5,4 1H	5,9—6,2 1H	6,7—7,3 10H	$CDCl_3$
Xb	1,6; 2,0 3H; 3H	3,3; 3,8 2H	5,25—5,5 1H	6,0—6,2 1H	6,5—7,3 10H	$CDCl_3$
XIa	1,7 3H	3,1; 3,25 2H	5,1—5,4 2H	5,9—6,2 1H	6,7—7,2 10H	CF_3COOH
XIb	1,65 3H	3,56; 3,8 2H	5,1—5,4 2H	5,9—6,2 1H	6,7—7,2 10H	CF_3COOH
XIIa	—	3,3 2H	5,3—5,55 2H	6,4—6,6 2H	6,8—7,3 10H	CF_3COOH
XIIb	—	3,7 2H	5,8—6,0 2H	6,9—7,1 2H	7,4—7,9 10H	CF_3COOH
XIIIa	1,7—2,2 7H	3,2; 3,5 2H	4,9—5,2 1H	—	6,8—7,4 10H	CF_3COOH
XIIIb	1,9—2,2 7H	3,5 2H	4,9—5,1 1H	—	7,2—7,7 10H	CF_3COOH

The configurations were established on the basis of PMR spectroscopic data. We assigned syn-configurations to IXa-XIIa and anti-configurations to isomers IXb-XIIb on the basis of the fact that the signals of the two protons attached to the C_2 and C_3 atoms of adducts IXa-XIIa, as a consequence of the anisotropy of the double bond, which is spatially close to these protons, are observed at stronger field as compared with the signals of the corresponding protons in adducts IXb-XIIb [7-9] (see Table 2).

For additional confirmation of this conclusion we studied the mass spectra of IXa,b-XIIa,b and compared them with the mass spectra of saturated analogs XIIIa,b, viz., 1-methyl-7,8-diazabicyclo[2.2.2]octane-2,3,7,8-tetracarboxylic acid bis-N-phenylimides, which were obtained by hydrogenation of both IXa and IXb isomers in the cold over a $Pd/CaCO_3$ catalyst.

The molecular ions of IXa,b-XIIIa,b that are formed under the influence of electron impact undergo fragmentation via three principal pathways, two of which are retrodiene cleavages of the cyclohexene (RDC_1) and diazacyclohexene (RDC_2) rings with the formation of the corresponding F_1 and F_2 ions (see Scheme 2). The third fragmentation pathway is cleaved of the molecular ion to give 2,5-dihydroxy-4-phenyl-1,2,4-triazoline and N-phenylphthalimide (177)* ion radicals (the F_3 and F_4 ions). This process suggests double migration of a hydrogen atom (the McLafferty rearrangement). The subsequent fragments of the F_1 and F_2 ions involves splitting out of isocyanate and CO molecules, which leads to F_5 and F_6 ions (119 and 91) (see Table 1).

Scheme 2



*In the text and in Scheme 2 the numbers that characterize the ions are the mass-to-charge (m/z) ratios.

TABLE 3. Relative Intensities of the Peaks of the F_1-F_3 Characteristic Ions (Σ50%)

Compound	W_M	F_1	F_2	F_3	$I_{F_1}/I^*_{M^+}$	$I_{F_2}/I^*_{M^+}$	$I_{F_3}/I^*_{M^+}$
IXa	3,6	32	0,4	1,1	9,0	0,1	0,3
IXb	1,2	30	0,9	0,4	30,0	0,9	0,6
Xa	0,4	13	0,8	2,1	30,0	1,3	6,0
Xb	0,65	23	0,8	0,6	32,0	2,6	1,0
XIa	2,5	21	0,2	0,7	8,6	0,06	0,3
XIb	3,5	24	1,0	0,2	1,0	0,2	0,05
XIIa	3,7	22	0,3	5,0	5,9	0,06	1,2
XIIb	2,7	21	0,8	0,3	8,0	0,3	0,1
XIIIa	4,0	17	1,5	0,7	4,4	0,4	0,2
XIIIb	7,0	12	3,5	0,2	1,7	0,5	0,03

*The I_{F_n}/I_{M+} values are the ratios of the intensities of the peaks of the F_n and M^+ ions.

The differences in the mass-spectral behavior of stereoisomeric pairs a and b affect only the relative intensities of the peaks of the characteristic ions. The stabilities of their molecular ions differ only slightly and do not make it possible to establish their configurations unambiguously (see Table 3). Considerably more appreciable differences are observed in the intensities of the peaks of the F_2 and F_3 fragment ions; the intensities of the F_2 ion peaks are always higher for the syn-isomers. This is associated, on the one hand, with the greater steric strain in the case of the syn-isomer, which usually promotes more intensive retrodiene cleavage of the molecular ions [10], and, on the other, with the fact that the anti-isomer, due to orbital interactions between the π electrons of the carbonyl groups of the maleinimide fragment and the p orbitals of the π bond, should be more stable, which leads to lower probability of the RDC_2 process. At the same time, the intensities of the F_3 ion peaks are higher for the anti-isomers. This difference is readily explained by the fact that in the case of the anti-isomers McLafferty rearrangement with the transfer of hydrogen atoms from the 2 and 3 positions to the oxygen atoms of the carbonyl groups of the triazoline ring, which leads to the formation of F_4 ions, is more readily realizable.

Of the hydrogenated XIIIa,b, the syn-isomer (XIIIa) is more stable (due to the p–π secondary orbital interaction between the π orbitals of the carbonyl groups and the p orbitals of the nitrogen atoms). However, in this case also the intensities of the F_2 ion peaks are higher for the syn-isomers.

Thus a study of the mass spectra of IXa,b-XIIIa,b showed that when both stereoisomers are present, one can draw a confident conclusion regarding their configurations, since the syn-isomers are characterized by higher (as compared with the anti-isomers) intensities of the F_2 ion peaks and lower intensities of the F_3 ion peaks. At the same time, an analysis of the mass spectra of only one of the isomers of the examined series does not make it possible to determine its configuration. Let us note that the presence of methyl groups in the 1, 5, and 6 positions does not have a substantial effect on the mass-spectral differences of the stereoisomers.

Thus on the basis of the data obtained it may be concluded that none of the investigated reactions of 1,3-cyclohexadienes V-VII with PTD proceeds stereoselectively with the formation of two stereoisomers, the ratio of which depends on the presence and position of the methyl groups in the starting 1,3-cyclohexadiene. 1,3-Cyclohexadienes with substituents at the ends of a conjugated system of multiple bonds gave primarily syn-isomers XIa and XIIa (the syn/anti ratio was ∿4:1), which are obtained in the case of approach of the dienophile from the most sterically hindered side. Kalo and Ginsburg [7] explain this sort of effect, which was previously observed in reactions of propellanes with PTD, by additional stabilization of the syn transition state as a consequence of secondary orbital interactions of the π orbitals of the carbonyl groups of the N-phenylimide fragment with the p orbitals of the nitrogen atoms of the dienophile.

The presence of a methyl group at the end of the conjugated cyclohexadiene system, by increasing the steric hindrance during orientation of the components, equalizes the above-described nonvalence interactions and determines the lower stereoselectivity of the reactions (the ratios of the isomers range from 1:1 to 1:1.5).

Thus, our previously discovered effect of methyl groups at the ends of the conjugated systems of double bonds in 2-pyrones and 2-pyridones on the endo-exo stereoselectivity of the diene synthesis with these hyterocyclic dienes [2,4,5] is also manifested in the reactions of 1,3-cyclohexadienes with PTD.

EXPERIMENTAL

The PMR spectra of solutions of IXa,b-XIIa,b in trifluoroacetic acid and of V-VIII in deuterochloroform were recorded with a Varian T-60 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with a Varian MAT-112 spectrometer at an ionization energy of 50 eV and at temperatures close to the melting points of the samples.

The starting monoadducts (I-IV) were obtained by the methods in [4, 5]. 3-Methyl- and 4-methyl-1,2-dihydrophthalic acid N-phenylimides (V, VII) and 1,2-dihydrophthalic acid N-phenylimide (VIII) were obtained by thermolysis of adducts I, III, and IV, respectively, by the method in [3].

3,4-Dimethyl-1,2-dihydrophthalic Acid N-Phenylimide (VI). A 0.3 g (1.05 mmole) sample of the adducts of 5,6-dimethyl-2-pyrone with PMI (II) was refluxed in 5 ml of toluene for 10 h, after which the solvent was evaporated in vacuo, and the residue was reprecipitated from solution in chloroform by means of petroleum ether to give 0.24 g (97%) of diene VI with mp 103-104°C (from ethanol). PMR spectrum (in $CDCl_3$): 2.1 (s, 3H, 6-CH_3), 2.3 (s, 3H, CH_3), 3.9-4.2 (m, 2H, 1-H, 2-H), 5.9-6.4 (m, 2H, 5-H, 6-H), and 7.4-8.0 ppm (m, 5H, aromatic). Found: C 76.0; H 5.3; N 5.6%. $C_{16}H_{14}NO_2$. Calculated: C 76.2; H 5.6; N 5.6%.

syn- and anti-7,8-Diazabicyclo[2.2.2]oct-5-ene-2,3,7,8-tetracarboxylic Acid Bis-N-phenylimides (IXa,b-XIIa,b). These compounds were obtained by the reaction of equimolar amounts of PTD and dienes V-VIII at 20°C in solution in methylene chloride. After evaporation of the solvent, the reaction mixtures were separated by chromatography with a column filled with silica gel (elution with chloroform). Two stereoisomeric adducts IXa,b-XIIa,b were isolated in each case (see Tables 1 and 2).

1.Methyl-7,8-diazabicyclo[2.2.2]octane-2,3,7,8-tetracarboxylic Acid Bis-N-phenylimides (XIIIa,b). These compoundswere obtained by hydrogenation over $Pd/CaCO_3$ of 0.3 g (0.72 mmole) of stereoisomeric bisimides IXa,b in 50 ml of methanol at 20°C for 2 h. The catalyst was then removed by filtration, the solvent was evaporated, and the residue was recrystallized (see Tables 1 and 2).

LITERATURE CITED

1. V. S. Pilipenko,and N. P. Shusherina, Zh. Org. Khim., 17, 2122 (1981).
2. N. P. Shusherina, Usp. Khim., 43, 1771 (1974).
3. N. P. Shusherina, T. L. Nesterova, and O. V. Polyakova, Zh. Org. Khim., 16, 1285 (1980).
4. N. P. Shusherina, Mohamed Haus Hakimi, V. S. Deeva, and L. V. Betaneli, Zh. Org. Khim., 11, 1966 (1975).
5. M. V. Gapeeva, A. Yu. Stepanyants, N. P. Shusherina, Yu. A. Knirel', and R. Ya. Levina, Zh. Org. Khim., 7, 2426 (1971).
6. A. Evnin, D. Arnold, L. Karnischny, and E. Strom, J. Am. Chem. Soc., 92, 6218 (1970).
7. J. Kalo and D. Ginsburg, Tetrahedron, 34, 2155 (1978).
8. J. Kazan and F. Greene, J. Org. Chem., 28, 2965 (1963).
9. P. Ashkenazi, D. Ginsburg, G. Schart, and B. Fuchs, Tetrahedron, 33, 1345 (1977).
10. V. G. Zashkin and N. S. Vul'fson, Khim. Geterotsikl. Soedin., No. 11, 1443 (1978).