SYNTHESIS OF SUBSTITUTED N-AMINOISOMALEINIMIDES

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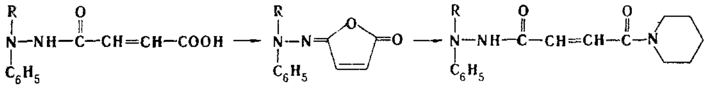
β,β-Disubstituted monohydrazides of maleic acid form stable aminoisomaleinimides on treatment with acetic anhydride in the presence of anhydrous sodium acetate. The structure of the products was confirmed by IR and PMR spectroscopy and by chemical methods.

The assumption of the isomerism of N-substituted maleinimides was first stated by Piutti [1], but the first papers on the synthesis of isoimides appeared only recently [2-4]. N-Arylisomaleinimides were obtained by dehydration of the corresponding monoamides of maleic acid by means of acetic anhydride under mild conditions [2, 3] and also by means of dicyclohexylcarbodiimide and ethyl chloroformate [4]. The dehydration of N-substituted monoamides of the corresponding acids with trifluoroacetic anhydride [5] should probably be considered to be a general and most convenient method for the synthesis of arylisomaleinimides and isophthalimides. However, N-arylisomaleinimides are obtained in low yields and are relatively easily isomerized to symmetrical arylmaleinimides. In addition, only a small number of isoimides were obtained by the methods mentioned above. These are probably the reasons for the small amount of study devoted to isomaleinimides. Some recent papers [5-7] were devoted primarily to the study of isophthalimides.

We have obtained exclusively stable disubstituted N-aminoisomaleinimides IIa-c (Table 1) by the action of acetic anhydride on disubstituted hydrazides of maleic acid.



I a-c II a-c III a-c

a $R=C_6H_5$; b $R=CH_3$; c $R=C_6H_5CH_2$

Symmetrical aminomaleinimides are not formed even under severe conditions on heating to 90-95°C. From the synthetic conditions, it can be assumed that the dimethylaminomaleinimide and N-morpholinomaleinimide described in the patent literature [8, 9] are actually the iso forms. The iso structure of the compounds that we obtained (IIa-c) is confirmed by the presence in their IR spectra of two very strong bands at 1760-1770 cm^{-1} ($\nu_{C=O}$) and 1730-1740 cm^{-1} ($\nu_{C=N}$), while the symmetrical maleinimides have a single very strong carbonyl absorption band at 1710-1720 cm^{-1}. The presence of two bands in the carbonyl absorption region has been noted by a number of investigators [4, 5, 10] as a characteristic distinguishing feature of isoimides. The PMR spectra of IIa and IIb have a doublet at ~6.0 ppm, which is associated with ethylene protons (IIa δ 5.88 ppm, IIb δ 6.01 ppm), and a second doublet is overlapped by the signals of the aromatic protons. Nevertheless, the branching of the signal of the ethylene protons serves as an indisputable proof of their nonequivalence; i.e., it confirms the isoimide structure of II. The spin-spin coupling constant ($J = 6$ Hz) corresponds to a cis orientation of the ring ethylene protons.

A characteristic reaction of isoimides is the reaction with piperidine [5], which leads to ring opening; under the same conditions, piperidine adds to the double bond of imides. This reaction proceeds readily with isoimides in the cold and in ether solution to give high yields; one should note the pronounced dependence of the rate of this reaction on R, which decreases in the order $R = C_6H_5 > R = CH_3 > R = C_6H_5CH_2$ approximately in a ratio of 1 : 5 : 50. The higher reactivity of the carbonyl group of isomaleinimides with

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C	Empirical formula	Found, %			Calc., %			IR spectrum, ν, cm^{-1}			Yield, %
			C	H	N	C	H	N	C=O	C=N	NH	
Ia	142—143[a]	$C_{16}H_{14}N_2O_3$	67,5	5,2	9,7	68,1	5,0	9,9	1715, 1670	—	3250 s	63
IIa	89—90[b]	$C_{16}H_{12}N_2O_2$	72,5	4,7	10,6	72,7	4,5	10,6	1768 vs	1735 vs	—	97
IIb	91—92,5[b]	$C_{11}H_{10}N_2O_2$	65,0	5,2	13,8	65,4	4,9	13,8	1754 vs	1742 vs	—	82[d]
IIc	113—113,5[c]	$C_{17}H_{14}N_2O_2$	73,1	5,4	10,1	73,4	5,0	10,0	1762 vs	1746 vs	—	79[d]
IIIa	173—175[a]	$C_{21}H_{23}N_3O_2$	72,4	6,5	11,9	72,2	6,6	12,0	1690 s	—	3160 m br	92
IIIb	143—144[a]	$C_{16}H_{21}N_3O_2$	61,9	7,1	13,6	62,5	6,9	13,6	1685 s	—	3238 vs, br	88
IIIc	135—135,5[a]	$C_{22}H_{25}N_3O_2$	72,3	7,0	11,7	72,7	6,9	11,5	1680 s	—	3240 m br	66

[a] From benzene. [b] From cyclohexane. [c] From ethanol. [d] Based on the starting hydrazine.

respect to the action of nucleophilic agents as compared with maleinimides is completely regular, since the CO—O bond has about the same character as in anhydrides. This reaction expands the possibility of the synthesis of amide hydrazides of maleic acid (Table 1) that are difficult to obtain by other methods. The IR spectra are in agreement with the structures of the compounds obtained.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrophotometer. The PMR spectra of CCl_4 solutions were recorded with a Varian 100 spectrometer with tetramethylsilane as the standard. The melting points given are uncorrected. The purity and individuality of the substances were verified by thin-layer chromatography on LS_{254} 5/40 μ silica gel in chloroform.

Maleic Acid Monohydrazides (I). A solution of an equimolecular amount of N,N-disubstituted hydrazine in 50 ml of benzene was added by drops with stirring to a solution of 0.1 mole of maleic anhydride in 150 ml of benzene at such a rate that the temperature of the reaction mass did not rise above 35°; the mixture was then stirred for 1 h. Monohydrazide Ia was removed by filtration, washed with benzene, and recrystallized from benzene—acetone (2 : 1) (see Table 1). Liquid monohydrazides Ib,c were separated from the upper benzene layer, washed with benzene, and used for the cyclization without purification. Compound Ia was obtained as a light-yellow crystalline substance that forms a hydrate during crystallization from aqueous solvents.

N-Aminoisomaleinimides (II) (Table 1). A 1-mole sample of monohydrazide I was mixed with a fivefold excess of acetic anhydride and 0.5 mole of anhydrous sodium acetate. When the mixture was stirred, it warmed up spontaneously and became bright red-orange. When the temperature began to fall, the mass was heated to 70-80° and stirred at this temperature for 40-60 min, after which it was cooled and poured into 2500 ml of ice water. The aqueous mixture was stirred for 0.5 h, and the liquid was decanted from the oily viscous precipitate. A total of 1 liter of a 3-5% solution of sodium carbonate was added to the precipitate, and the mixture was stirred for 0.5 h. The resulting solid was washed with water and dried at room temperature. Isoimides IIa-c were obtained as light-yellow readily crystallizable substances that are readily soluble in most organic solvents.

Maleic Acid Piperidide Hydrazides (III) (see Table 1). A 0.01-mole sample of piperidine was added to a solution of 0.01 mole of isoimide in 50 ml of diethyl ether, and the mixture was allowed to stand at room temperature for 12 h. The colorless precipitate was washed with ether, dried, and crystallized from benzene.

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