1-ETHYLTHIO-2R-ISOINDOLES.

AN EXAMPLE OF NONSYNCHRONOUS ADDITION IN THE DIELS-ALDER REACTION

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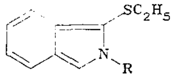
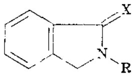
The previously unknown 1-ethylthio-2R-isoindoles have been obtained by modifying the corresponding isoindol-1-ones. The reaction of these isoindoles with N-arylmaleimide derivatives has been investigated. A rare case of nonsynchronous addition in the Diels-Alder reaction has been found.

In 1975, a sensitive method of determining amino groups in biological material was proposed [1], which consisted in the treatment of amino acid, peptides, or proteins with phthalaldehyde in the presence of alkanethiols. It is known that the 2-alkyl-1-alkylthioisoindoles formed in the course of the reaction of the reagent with the amino group of the substrate are responsible for the fluorescence of the reaction products [2, 3]. In a number of special experiments, when the reagent was treated with primary amines, intensive fluorescence was observed but it was possible to isolate and characterize the individual 2-alkyl-1-alkylthioisoindoles in only three cases [3, 4].

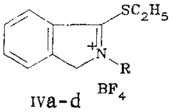
In the present paper we describe a method for obtaining the previously unknown 1-ethylthio-2R-isoindoles (I) by the successive chemical modification of the corresponding isoindol-1-ones (IIa-d). The first stage was the synthesis of the thiones (IIIa-d), which have not been described in the literature, by boiling the isoindole-1-ones (IIa-d) with phosphorus pentasulfide in pyridine (1-2 h). The isoindole-1-thiones are light yellow (IIIa, b) or yellow-green (IIIc, d) crystalline substances information on which is given in Table 1.



Ia-d



IIa,d,IIIa-d



IVa-d

I—IV a $R=CH_3$, b $R=C_6H_5$, c $R=4'-CH_3C_6H_4$, d $R=4'-CH_3OC_6H_4$; II X=O; III X=S

In the UV spectra of each of the thiones (III) both long-wave bands were shifted bathochromically in comparison with those in the corresponding isoindol-1-ones. A comparison of the PMR spectra of compounds (II) and (III) showed a paramagnetic shift of the resonance absorption of the proton-containing groups of the aryl substituent and of the $3-CH_2$ methylene group. This shift may amount to a magnitude of 0.4 ppm. In the IR spectra of compounds (IIIa-d) there were no absorption bands in the 1600-1800 cm^{-1} region. In solutions of the isoindol-1-thiones, one may a priori assume the presence of the tautomeric 1-mercaptoisoindoles, but the features of their PMR spectra in solvents with different polarities indicate the thioamide structure of the substances synthesized.

The next stage of the synthesis of (I) consisted of the S-alkylation of the isoindole-1-thiones (III). It is known [5] that the alkylation of secondary thioamides takes place at the sulfur atom with the formation of the corresponding thionium salts. Attempts to alkylate (III) with dimethyl sulfate or alkyl halides proved to be unsuccessful. The formation of the thionium salts (IVa-d) was observed when solutions of the thione (IIIa-d) in chloroform were added to a solution of Meerwein's reagent and the reaction mixture was kept in the cold for 1 day. The thionium salts consisted of light pink crystalline substances readily decomposing on heating. The frequency of the stretching vibrations of C=S bond, appearing close to 1100 cm^{-1} in the initial thiones, had disappeared in the spectra of the thionium

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TABLE 1. Constants and Spectral Characteristics of Compounds (I-V)

Compound	mp*, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectra, ν, cm⁻¹†		R_f	Found, %		Empirical formula	Calculated, %		Yield, %
			$C{=}C_{arom}$	C=X		N	S		N	S	
Ib		203 (4,42), 214 (4,31), 236 (4,32), 287 (3,54), 300 (3,37), 340 (3,35)	1595, 1500		0,69	5,7	12,4	$C_{16}H_{15}NS$	5,5	12,6	45
Id	120—122	203 (4,33), 223 (4,43), 246 (4,29), 287 (3,59), 300 (3,46), 340 (3,61)	1580, 1500		0,70	5,1	10,9	$C_{17}H_{17}NOS$	4,9	11,3	50
IIIa	179—181	204 (4,39), 256 (4,00), 306 (4,00)	1595, 1500	1090	0,50	8,7	19,3	C_9H_9NS	8,6	19,6	55
IIIb	114—115	203 (4,46), 266 (4,11), 294 (3,87), 329 (3,87)	1600, 1500	1100	0,64	6,3	14,3	$C_{14}H_{11}NS$	6,2	14,2	53
IIIc	128—129	205 (4,53), 246 (4,02), 270 (4,10), 329 (3,86)	1595, 1505	1095	0,66	6,0	13,5	$C_{15}H_{13}NS$	5,8	13,4	54
IIId	105—106	203 (4,69), 246 (4,20), 280 (4,18), 329 (3,92)	1580, 1510	1100	0,67	5,7	12,3	$C_{15}H_{13}NOS$	5,5	12,5	70
IVa	123—125	244 (4,36), 300 (3,70), 312 (3,79), 322 (3,83), 330 (3,66)	1610, 1595	1550	0,69	4,8	11,4	$C_{11}H_{14}BF_4NS$	5,0	11,5	80
IVb	173—175	248 (4,37), 292 (3,74), 304 (3,65), 344 (3,77)	1610, 1595	1520	0,71	4,0	9,3	$C_{16}H_{16}BF_4NS$	4,1	9,4	60
IVc	145—147	244 (4,05), 277 (3,86), 360 (3,18), 380 (3,12)	1610, 1595	1515	0,73	4,1	9,1	$C_{17}H_{18}BF_4NS$	3,9	9,0	58
IVd	99—100	243 (4,03), 277 (3,80), 355 (310), 380 (3,00)	1605, 1595	1515	0,75	3,9	9,1	$C_{17}H_{18}BF_4NOS$	3,8	8,6	50
Va	150—153	206 (4,38), 227 (4,52), 253 (3,78), 336 (3,68), 345 (3,60)	1510, 1460	1770 1710	0,21	7,3	8,0	$C_{22}H_{22}N_2O_3S$	7,1	8,1	90
Vb	140—142	206 (4,57), 234 (4,31), 289 (3,39), 300 (3,31), 336 (3,27)	1600, 1520	1770, 1720	0,48	6,3	7,3	$C_{27}H_{24}N_2O_3S$	6,1	7,0	90
Vc	164—166	206 (4,58), 234 (4,35), 289 (3,45), 300 (3,32), 336 (3,32)	1600, 1510	1770, 1710	0,61	6,3	6,9	$C_{28}H_{26}N_2O_3S$	6,0	6,8	90
Vd	135—137	206 (4,54), 222 (4,51), 244 (4,35), 289 (3,88), 300 (3,78), 336 (3,68)	1600, 1500	1770, 1710	0,54	6,0	7,3	$C_{27}H_{24}N_2O_3S$	6,1	7,0	90

*(Ib) formed a viscous oil; (Id) and (IIIa-d) were recrystallized from ethanol.

†(IIIa-d): X = S; (IVa): $X{=}\overset{+}{N}\langle$; dienophilic fragment of the adducts (Va-d), X = O.

salts. At the same time, a new band had appeared close to 1520-1550 cm^{-1} belonging to the vibrations of a $\rangle C{=}\overset{+}{N}\langle$ bond. In addition, the structure of the thionium salts were confirmed by their PMR spectra, in each of which, in addition to the singlet of the 3-CH_2 methylene group, the signals of a S-ethyl grouping were clearly shown. While treatment of the thionium salts (IVa-d) with a dilute solution of an alkali led to their rapid decomposition with the elimination of ethyl mercaptan, sublimation in vacuum of a mixture of, for example, the salt (IVd) with carefully ground solid alkali gave 2-(4'-anisyl)-1-ethylthioisoindole (Id) in the form of acicular light yellow crystals. With the aid of this expedient, from the salts (IVb, c) the isoindoles (Ib, c) were obtained in the form of a viscous light yellow oil on the cooled part of the instrument for sublimation. All the isoindoles (Ib-d) were substances extremely unstable in air. The most stable compound of this series proved to be the isoindole (Id), which, like substance (Ib), was analyzed and characterized spectrally, but unlike the latter was a crystalline substance with a definite melting point. An attempt to

TABLE 2. PMR Spectral Characteristics of the Adducts (Va-d)

Compound	Chemical shifts, δ, ppm											SSCCs of the protons, J, Hz				
	CH_3—X (X=O, N)	4-H	5-H	6-H	S—CH_2CH_3		aromatic protons					4-H—5-H	5-H—6-H	*	†	S—CH_2CH_3
					CH_2	CH_3	H_A	H_B	H_{C-F}	H_G	3-H					
Va	s, 2,18 (6H)	d, 4,64	d.d, 3,85	d, 3,58	q, 2,70	t, 1,29	d, 6,25	d, 6,94	7,26			5,4	8,4	8,4		7,3
Vb	s, 2,17 (3H)	d, 5,25	m, 3,99—3,68		m, 2,58	t, 1,16	d, 6,25	d, 6,95		m, 7,43—7,05		3,4				7,5
Vc	s, 2,18 (6H)	d, 5,21	m, 3,92—3 76		m, 2,59	t, 1,17	d, 6,25	d, 7,07	7,16—7,42	d, 6,93	d, 6,97	4,9		8,4	3,5	7,3
Vd	s, 3,60 (3H)	d, 5,13	d.d 3,82	d, 3,88	m, 2,56	t, 1,16	d, 6,70	d, 7,01	7,19—7,44	d, 6,38	7,08—7,19	4,3	17,5	8,4	3,5	7,3

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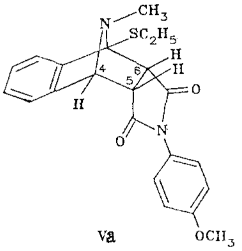
*ortho-SSCCs of the protons of the N-aryl substituent from the dienophile.

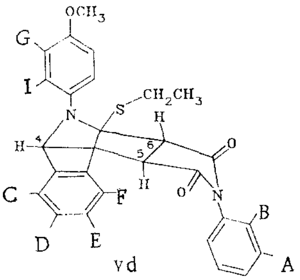
†ortho-SSCCs of the protons of the N-aryl substituent of the diene (isoindole).

isolate the isoindole (Ia) from the salt (IVa) by this method proved unsuccessful: when the mixture with alkali was heated, decomposition took place.

All the isoindoles (Ib-d) gave a positive Ehrlich test and were characterized by the presence of long-wave absorption in the 320-360 nm region. A standard procedure in isoindole chemistry is the identification of unstable compounds via the adducts of the Diels-Alder reaction with maleimide derivatives [6]. The configurations of the adducts are determined on the basis of the SSCCs of the 1-H, 4-H, 5-H, and 6-H protons of the 7-azabenzonorbornene system [7]. In the case of the 1,2-disubstituted isoindoles, however, the complete analysis of the SSCCs and chemical shifts of the proton-containing groupings of the possible (1:1) adducts is considerably complicated by virtue of the nonequivalence of the 5-H and 6-H protons. We isolated and characterized four adducts of maleimide with the isoindoles (Ia-d) having the 1:1 composition. Details of their PMR spectra are given in Table 2, and an analysis of their electronic spectra unambiguously showed that the substances that we had isolated were adducts of Michael type, since they lacked the long-wave isoindole absorption that is characteristic for structures of type (I). Following the general opinion that a Diels—Alder reaction of the $[\pi^4 s + \pi^2 s]$-cycloaddition type takes place by a synchronous mechanism, it was possible to assume the formation of the corresponding exo or endo adducts. Thus, a comparison of the magnitudes of the observed vicinal SSCCs (see Table 2) with their values calculated by means of the Karplus and the Williams—Johnson formulas [8] permitted compound (Va) to be assigned to adducts with the endo configuration. The PMR spectrum of the adduct (Vd) contained a multiplet in the 3.94-3.74 ppm region which consisted of the superposition of a doublet of doublets with its center at 3.82 from the 5-H proton and a doublet with its center at 3.88 ppm from the 6-H proton, and in a weaker field there was a doublet relating to the 4-H proton; i.e., superficially the pattern resembled the spectrum of the endo isomer [compound (Va)]. However, the excessively high value of the J_{5-6} constant, 17.5 Hz, put us on guard. Such a high SSCC may, according to calculations by the Karplus and Williams—Johnson formulas, be observed for vicinal protons located in a single plane in different directions (dihedral angle φ = 180°) and, judging from the values of the J_{4-5} SSCCs, of the two trans isomers possible according to the first statement, we had isolated that in which the dihedral angle between the 4-H and 5-H protons was 120°, and not 65°, i.e., on the basis of an analysis of its PMR spectrum the adduct (Vd) must be assigned the structure:



Va



Vd

The formation of an adduct with the structure (Vd) cannot be explained on the basis of ideas concerning a synchronous mechanism of cycloaddition controlled by orbital symmetry (the Woodward—Hoffman rules). Consequently, here we are dealing with a rare case of the nonsynchronous occurrence of the Diels—Alder reaction, which is connected with the substantial steric hindrance in the molecule of the initial isoindole, i.e., with the presence of the ethylthio group and the aryl substituent.

The PMR spectra of compounds (Vb) and (Vc) each contain a doublet ascribed to the resonance of the 4-H proton and a multiplet from the 5-H and 6-H protons. This multiplet possibly represents the superposition of a doublet of doublets and a doublet, as in the case of compound (Vd). Even on an instrument with a working frequency of 200 MHz, a stretching out of the signals of the multiplet did not lead to the determination of the values of the necessary SSCCs. The J_{4-5} constant was calculated from the doublet due to the 4-H proton. However, since the J_{5-6} constant was not determined, it was impossible to draw a definitive conclusion concerning the configuration of the adducts. It is clear only that they did not belong to the exo series. Nevertheless, on the basis of the closeness of the chemical shifts of the protons of the ethylthio group and those of 4-H, 5-H, and 6-H in compounds (Vb) and (Vc) to the corresponding shifts for (Vd), it may be assumed that these compounds were also formed as the result of nonsynchronous cycloaddition.

Of the other features of the PMR spectra of the adducts (V), we must mention the anomalously large upfield shift of the signals of the methyl groups attached to the nitrogen and oxygen atoms. This is due to the screening of the methyl protons by the aromatic rings. It is interesting that in compound (Va) the N- and O-methyl groups, and in compound (Vc) the C- and O-methyl groups, give common signals (in the form of singlets) corresponding to six proton units. In the adducts (Va-d), the protons of the methylene group included in the S-ethyl substituent are potentially diastereotopic. In the absence of a magnetically anisotropic group at the bridge nitrogen atom [compound (Va)], the protons of the CH_2 group will behave as equivalent and appear in the form of a quartet. A different pattern was observed for compounds (Vb-d), in which the protons of the CH_2 group behave as nonequivalent in view of the close possession of a magnetically anisotropic group — an aromatic ring. In these compounds, the signal from the protons under consideration appeared in the form of a multiplet representing the superposition of two quartets from the two nonequivalent protons of the S-ethyl group. The case described of a multiplet from the CH_2 group in an ethyl grouping when a magnetically anisotropic substituent is close to it is not unique. A similar phenomenon has been observed previously; for example, in [9]. The signal of the methyl group of the $S-C_2H_5$ grouping in compound (Va) appeared in the form of a pure triplet, while in the other compounds it had a small additional splitting, which corresponds to the explanation adopted above.

EXPERIMENTAL

Corrected values of the melting points were determined on a Boëtius instrument. The individuality of the substances was established with the aid of TLC on Silufol plates with benzene—ethanol (9:1) as eluent. UV spectra were recorded on a Specord UV-vis spectrophotometer using $5 \cdot 10^{-5}$ M solutions of substances (Ib-d), (IIIa-d), and (Va-d) in ethanol and of compounds (IVa-c) in chloroform. IR spectra were recorded on a Specord IR-71 instrument using tablets of the substances under investigation with KBr. The PMR spectra of compounds (IIIa-d) and (IVa-c) were taken on a ZKR-60 instrument with a working frequency of 60 MHz, and those of compounds (Va-d) on a Bruker instrument with a working frequency of 200 MHz. The spectra of the salts (IVa-c) were recorded for solutions in CF_3COOH, and those of the other compounds in $CDCl_3$. TMS was used as internal standard.

The isoindol-1-one (IIa) with mp 158°C was obtained by the method of Brewster et al. [10]. According to the literature [10], mp 157°C. Compounds (IIb-d) were synthesized by a method described previously [11].

N-Phenylmaleimide was synthesized by the method of Tawney et al. [12] with a yield of 80-95%, mp 89-90°C according to the literature [12]. mp 90°C. N-(4'-Methoxyphenyl)maleimide was obtained by the method of Ivanov et al. [13] with a yield of 80-90%, mp 148°C; according to the literature [13]; mp 147-149°C.

The Isoindole-1-thiones (IIIa-d). To a carefully ground mixture of 10 mmole of the appropriate phthalimidine and 6 mmole of phosphorus pentasulfide was added 300 mmole of dry pyridine, and the reaction mixture was heated at 140-150°C (bath temperature) for 1-2 h. The hot dark solution was poured into 100 ml of water, and the mixture was brought to pH 9 with a solution of potassium hydroxide and was left overnight. The crystals that had deposited were filtered off and washed with water. After drying, the preparation was purified by recrystallization from ethanol. PMR spectrum: s, 4.56 (IIIa) or 5.00-5.15 (IIIb-d) with an intensity of two proton units belonging to the 3-CH_2 group: d, 7.83, for (IIIa) or d.d, 8.16-8.31 for (IIIb-d), belonging to the 7-H proton.

The Thionium Salts (IVa-d). A solution of 5 mmole of Meerwein's reagent (obtained as given by Sandler and Karo [14], yield 85%, mp 90°C, according to [14], mp 91-92°C) in 120 mmole of chloroform was added dropwise to a solution of 15 mmole of the corresponding thiophthalimidine in 120 mmole of chloroform. The reaction mixture was kept at 0-5°C for 24 h, and the crystals that had deposited were filtered off and carefully washed with chloroform. The salts obtained were suitable without purification for elementary analysis and subsequent use. PMR spectrum: s, 5.25-5.51 (2 H), belonging to 3-CH_2; q, 3.98, for (IVa) or q, 3.2-3.3 for (IVb-d) — $S-CH_2$: t, 1.67 for (IVa) or t, 1.41 for (IVb-d), belonging to the methyl group of $S-C_2H_5$.

General Method for Obtaining the Isoindoles (Ib-d). A mixture of 10 mmole of the appropriate dry thionium salt (IV) and 10 mmole of dry alkali was ground. The homogeneous mass was placed in a vacuum sublimator. The N-arylisoindoles condensed on the cooled element in the vacuum of an oil pump (0.2 mm Hg) at a bath temperature of 150°C. Compounds (Ib and c) were viscous light yellow oils, and (Id) was in the form of light yellow crystals. The yields of the isoindoles by this method were not less than 45–50%.

Methods of Obtaining the Adducts (Va-d). To facilitate the interpretation of the PMR spectra of the adducts (Va-d), various dienophiles were used in their synthesis: for the isoindole (Id), N-phenylmaleimide; and for the others, N-(4'-methoxyphenyl)maleimide.

A. At room temperature, 5 mmole each of the appropriate isoindole and maleimide were mixed. Then 200 mmole of ethanol was added. After the reaction mixture had been kept at −5°C for 6 h, the precipitate was filtered off and washed with ethanol to give compounds (Vb-d).

B. A solution of 10 mmole of triethylamine in 200 mmole of ethanol was added to a carefully ground mixture of 10 mmole of thionium salt and 10 mmole of the appropriate maleimide. The reaction mixture was kept at −5°C for 6–8 h, and the resulting precipitate was filtered off and washed with ethanol.

By this method it was possible to obtain compounds (Va-d) suitable for elementary analysis without purification.

LITERATURE CITED

1. J. R. Benson and P. E. Hare, Proc. Natl. Acad. Sci. USA, 72, 619 (1975).
2. S. S. Simmons, Jr., H. L. Ammon, and R. Doherty, J. Org. Chem., 46, 4739 (1981).
3. S. S. Simmons, Jr. and D. F. Johnson, J. Am. Chem. Soc., 98, 7098 (1976).
4. S. S. Simmons, Jr. and D. F. Johnson, J. Org. Chem., 43, 2886 (1978).
5. R. N. Hurd and G. Delamater, Chem. Rev., 61, 45 (1961).
6. F. S. Babichev and V. A. Kovtunenko, The Chemistry of Isoindole [in Russian], Naukova Dumka, Kiev (1983).
7. V. A. Kovtunenko, Z. V. Voitenko, A. V. Turov, A. K. Tyltin, and F. S. Babichev, Ukr. Khim. Zh., 49, 1287 (1983).
8. R. M. Silverstein, G. C. Bassler, and T. Morrill, Spectrometric Identification of Organic Compounds, 3rd edn., Wiley, New York (1974).
9. P. J. Abbott, R. M. Acheson, M. I. Kornilov, and J. K. Stubbs, J. Chem. Soc., Perkin I, No. 12, 2322 (1975).
10. J. H. Brewster, A. M. Fusco, L. E. Carosino, and B. G. Corman, J. Org. Chem., 28, 498 (1963).
11. V. A. Kovtunenko, A. K. Tyltin, T. T. Dobrenko, and F. S. Babichev, Ukr. Khim. Zh., 49, 1099 (1983).
12. P. O. Tawney, R. H. Snyder, and C. E. Bryan, J. Org. Chem., 25, 56 (1960).
13. V. S. Ivanov, V. K. Smirnova, and T. I. Sidorova, Methods for Obtaining Chemical Reagents and Preparations [in Russian], IREA, Moscow, No. 15 (1967), p. 85.
14. S. R. Sandler and W. Karo, Organic Functional Group Preparations, Academic Press, New York, Vol. 3 (1971), Chapter 8.