SYNTHESIS AND SPECTRAL PROPERTIES OF PHTHALIMIDINES AND PHTHALIDES

A. P. Stankyavichyus, P. B. Terent'ev, and A. S. Anyulis

Alkaline hydrolysis of substituted 2-cyanocinnamic acids leads to the corresponding substituted 3-carboxymethylphthalimidines; acid hydrolysis of the same acids results in the formation of phthalides with an analogous structure. NMR and mass spectrometric data are examined critically.

Phthalimidines are convenient models for the synthesis of various derivatives of isoindole [1]. One of the possible paths for obtaining such synthons is the hydrolysis of o-cyanocinnamic acids [2], which have become relatively available compounds in recent years [3-5].

The ability of cis-cinnamic acid to isomerize upon heating in acids or alkalis to the more stable trans-isomer [6] and the comparative ease of hydrolysis of the cyano group in 2-cyanocinnamic acids [7], on the one hand, and the inertness to hydrolysis of o-substituted benzonitriles [8], on the other hand, led us to investigate the behavior of isomeric cis- and trans-2-cyanocinnamic acids in the presence of dilute acids and alkalis. We found that when the cis-cyano acids Ia-f were boiled for 2-3 h with a 10% aqueous solution of sodium hydroxide, the 3-carboxymethylphthalimidines IIa-e were obtained in good yields; only in the case of the benzoyl-substituted acid If did the final reaction product have the structure of trans-5-benzoyl-2-carboxycinnamic acid (III). When the acids Ia-f with a known trans-structure were brought into reaction under the same conditions, exactly the same reaction products were obtained.

Prolonged acid hydrolysis of either the cis or trans-acids Ia-f in 4.5-5% (1:7) hydrochloric acid gave the 3-carboxymethylphthalides IVa-e; however, boiling the cis acid Ia in still more dilute hydrochloric acid (3%, 1:10) [8] gave trans-2-carbamoylcinnamic acid V. All of these data suggest that the initial step in either an acetic or alkaline medium is isomerization of the cis isomers I to compounds with the trans-configuration at the double bond, with subsequent hydrolysis of the cyano group and heterocyclization of the hydrolysis products (Scheme 1).

TABLE 1. Properties of Phthalimidines IIb-e and Phthalides IVb-f

Compound	Heating time, h	t_{mp}, °C; solvent for crystalliza-	R_f	UV spectrum λ_{max}, nm (log ε)	Empirical formula	Yield, %
IIb	3	265 (dec.) water	0,20**	275(3,31)	$C_{10}H_9NO_4$	93
IIc	3	195-196; water	0,27*	294(3,62)	$C_{11}H_{11}NO_4$	83
IId	3	202-203;	0,25*	229(4,03), 273(3,94)	$C_{10}H_8BrNO_3$	71
IIe	2	227-228; ethanol	0,22*	236(4,01)	$C_{12}H_{14}N_2O_5S$	64
III	3	149-151; water	0,05*	—	$C_{17}H_{12}O_5$	81
IVb	12	223- water	0,23**	—	$C_{10}H_8O_5$	85
IVc	55	168-169 water	0,30*	300(3,50)	$C_{11}H_{10}O_5$	77
IVd	15	164-165, water	0,28*	232(3,92), 217(3,60)	$C_{10}H_7BrO_4$	89
IVe	36	210-211; ethanol	0,37*	234(3,86)	$C_{12}H_{13}NO_6S$	72
IVf	11	175-176; water	0,30*	264(4,04)	$C_{17}H_{12}O_5$	83

*On aluminum oxide.

**On paper.

M. V. Lomonosov Moscow State University. Z. Yanushkyavichyus Scientific-Research Institute of Physiology and Pathology of the Cardiovascular System, Kaunas. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 472-476, April, 1992. Original article submitted February 15, 1991.

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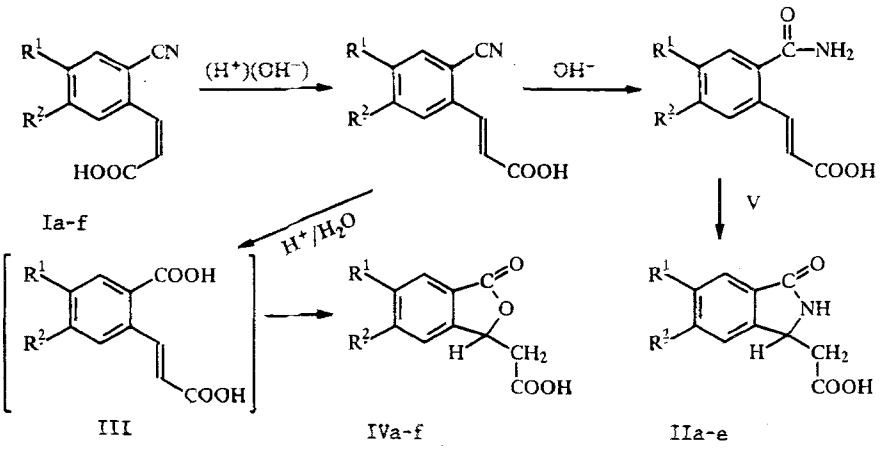
Scheme 1

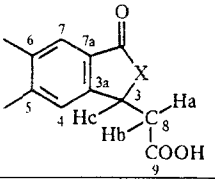


I-IVa, d, e, f) R^1 = H; b) R^1 = OH; c) R^1 = OMe; a, b, c) R^2 = H; d) R^2 = Br; e) R^2 = SO_2NMe_2; f) R^2 = COPh.

In the PMR spectra of compounds II and IV (Table 2), in the intermediate-field region, a typical pattern of signals of an ABX system is observed, characterizing the CH—CH_2—CO— grouping; and as expected, the chemical shifts of these protons (especially the methine protons) in the spectra of the phthalides are downfield from those in the spectra of the phthalimidines II.

Just as sharply different are the ^{13}C NMR spectra of the lactams and lactones (Table 3), particularly in the upfield region. The chemical shift of the methine carbon atom in the unsubstituted lactam IIa is 53.08 ppm, whereas in the spectrum of the lactone IVa, owing to the greater electronegativity of the oxygen atom, this signal is farther downfield (77.58 ppm). It is interesting to note that the chemical shifts of the cyclic carbonyl carbon atoms in the spectra of the lactams and lactones are practically identical (169.61 and 169.79 ppm, respectively). At the same time, the chemical shift of the carboxyl atom of the phthalimidine

TABLE 2. ^1H NMR Spectra of Compounds II and IV



Compound	X	^1H chemical shifts, δ, ppm, and multiplicity (and J, Hz)						
		H_a	H_b	H_c	H_4	H_5	H_6	H_7
IVb	O	2,58 dd	3,03 dd	5,72 dd	7,03 d (2,0)	7,10 dd (8,0; 2,0)	—	7,42 d (8,0)
IIb	NH	2,42 dd	2,69 dd	4,71 dd	6,97 d (2,0)	6,91 dd (8,0; 2,0)	—	7,34 d (8,0)
IVc	O	2,60 dd	3,07 dd	5,72 dd	7,20 d (2,0)	7,27 dd (8,0; 2,0)	—	7,52 d (8,0)
IIc	NH	2,45 dd	2,71 dd	4,75 dd	7,08 d (2,0)	7,10 dd (8,0; 2,0)	—	7,42 d (8,0)
IVd	O	2,95 dd	3,28 dd	5,93 dd	7,85 s	—	8,02 s**	
IId	NH	2,40 dd	2,93 dd	4,83 dd	—	—	7,39 s**	
IVe	O	2,72 dd	3,05 dd	5,78 dd	7,6 s	—	7,85 s**	
IIe	NH	2,49 dd	3,08 dd	4,86 dd	7,6 s	—	7,85 s**	
IVf	O	2,80 dd	3,18 dd	5,89 dd	7,3 s	—	7,9 m	

*In spectra of all compounds, $J_{a,b}$ = 16.0, $J_{a,c}$ = 8.0, and $J_{b,c}$ = 5.0 Hz.

**In the spectra of compounds IId, e and IVd-f, the signals of the aromatic protons are merged into one broad singlet (almost an unresolved multiplet) with integral intensity 2(3)H (in the spectra of compound IVf, 3H + 5H).

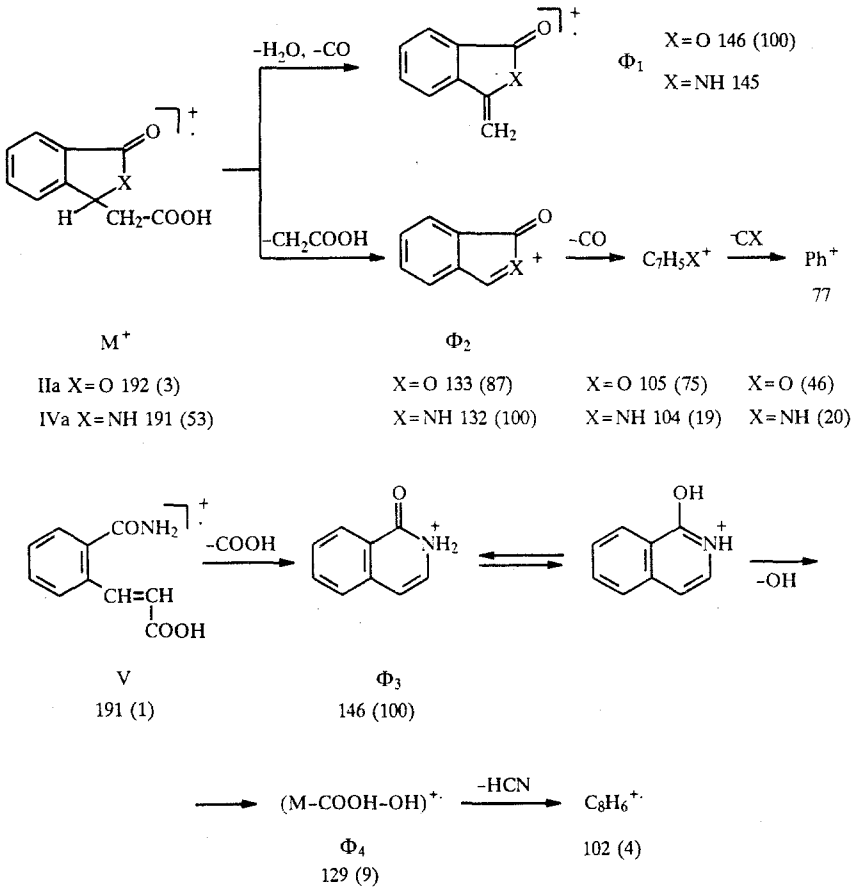
TABLE 3. ^{13}C NMR Spectra of Compounds IIa and IVa

Compound	^{13}C chemical shifts, δ, ppm									
	C_1	C_3	C_{3a}	C_4	C_5	C_6	C_7	C_{7a}	C_8	C_9
IIa	169,6	57,08	147,2	123,3	131,8	123,2	128,4	132,4	39,37	172,2
IVa	169,8	77,6	149,4	125,0	134,4	122,8	129,4	125,6	38,9	170,9

IIa is downfield from that of the phthalide IVa. This difference is probably related to the presence of an additional hydrogen bond in the lactams between the NH group and the carbonyl oxygen atom of the carboxyl group, since the values of pK_a of the phthalimidines IIa, d, e (4.30, 4.55, 4.95) are higher than for the corresponding phthalides IVa, d, e (4.10, 4.0, 4.80).

In the mass spectrum of compound IIa we observe an intense peak of the molecular ion (M^+) and also peaks of the ions Φ_1 and Φ_2 (Scheme 2), the latter being the most intense. Its formation is related to the predominant "amine" direction of decomposition of the molecular ion [9].

Scheme 2*



*Numbers characterizing the ions define the values of m/z.

The similar character of fragmentation also follows from an analysis of the mass spectrum of the phthalide IVa; in this case, however, the most intense peak is that of the ion Φ_1, whereas the loss of a carboxymethylene group (Φ_2) by the relatively unstable M^+ is somewhat less probable.

An entirely different set of ions characterizes the mass spectrum of the amide V, which is isomeric with the lactam IIa. Its unstable M^+ very readily eliminates a carboxyl group (the ion $[M - OH]^+$ is virtually absent) to form the ion Φ_3, which probably has a cyclic structure. Let us note that in this case we do not observe loss of the ortho-substituent (carbamoyl group) from M^+, which was so characteristic for ortho-substituted cinnamic acids [10]. In the total ion flux, the relative amount of

this ion alone is greater than 20%, indicating the high selectivity of decomposition. The subsequent fragmentation of the Φ_3 ion involves successive elimination of a hydroxyl group and a molecule of hydrocyanic acid.

Thus, alkaline or acid hydrolysis of substituted 2-cyanocinnamic acids can serve as a convenient preparative method in the synthesis of substituted phthalimidines and phthalides.

EXPERIMENTAL

The chromatographic separation of the acids II-IV was carried out on Leningrad B paper or by TLC on aluminum oxide (activity grade II) in a system consisting of isopropanol and 12.5% aqueous ammonia (4:1), with development by iodine vapor. The UV spectra were taken in ethanol in an SF-16 instrument. The ^{1}H NMR spectra were recorded in a Hitachi Perkin–Elmer instrument (90 MHz) in solution in DMSO-d_6, internal standard HMDS; the ^{13}C NMR spectra were recorded in a Tesla BS-567A instrument (25 MHz), in DMSO-d_6. The mass spectra were taken in an MAT-212 instrument (Varian) with a 70-eV ionization energy, with direct introduction of the sample into the ion source. The values of pK_a of the acids were determined potentiometrically.

The elemental analysis for C, H, N, S, and Br were in agreement with the calculated values.

Phthalimidines IIa-e. A solution of 5.2 g (0.03 mole) of the appropriate cis-acid I in 30 ml of a 10% sodium hydroxide solution was boiled for 2-3 h (see Table 1). The solution was cooled, filtered, and acidified with hydrochloric acid (Congo Red indicator). The precipitate was filtered off, washed with water, and dried. In the analogous alkaline hydrolysis of the trans-acids Ia-f, the phthalimidines IIa-e were also obtained with very similar yields.

trans-5-Benzoyl-2-carboxycinnamic acid (III) was obtained by boiling 0.14 g (0.0005 mole) of the cis-acid If in 3 ml of a 10% sodium hydroxide solution for 3 h. ^{1}H NMR spectrum: 7.22-8.1 (aromatic protons), 6.67 ppm (d, ethylene protons); a second doublet is superposed on the aromatic protons (J = 16 Hz).

Phthalides IVa-f. A solution or suspension of 5.2 g (0.03 mole) of the appropriate cis-acid I in 240 ml of dilute (1:7) hydrochloric acid (~4.5%) was boiled for 11-77 h (see Table 1), after which it was cooled, and the precipitate was filtered off, washed with water, and dried. By hydrolysis of the trans-acids Ia-f under analogous conditions, the same phthalimides IVa-f were obtained.

trans-2-Carbamoylcinnamic acid (V) was obtained by boiling 0.44 g (0.0025 mole) of the cyano acid Ia in 5.5 ml of dilute (1:10) hydrochloric acid (~3%) for 35 h, after which the precipitate was filtered from the hot solution and washed with water. R_f 0.31 (paper), mp 235-236°C (according to [8], mp 237°C). ^{13}C NMR spectrum: $C_{(1)}$ 138.1, $C_{(2)}$ 129.8; $C_{(3)}$ 126.9, $C_{(4)}$ 127.8, $C_{(5)}$ 129.9, $C_{(6)}$ 120.7; α-CH 141.9; β-CH 131.9; COOH 170.5; $CONH_2$ 167.7 ppm. Yield 0.32 g (63%).

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