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PREPARATIVE SYNTHESIS OF 7-CARBOXY-2-R-ISOINDOL-1-ONES

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A preparative method for the synthesis of 7-carboxy-2-R-isoindol-1-ones was developed on the basis of the [4+2] cycloaddition of secondary furfurylamines to maleic anhydride.

Keywords: isoindolones, furfurylamines, intramolecular Diels–Alder reaction.

Isoindolones, or phthalimides, can be obtained from phthalic anhydride [1] and various derivatives of phthalic acid [2, 3] by the oxidation of 2-R-1-methoxycarbonylisoindoles [4].

Functionally substituted isoindolones, from which various condensed heterocyclic systems containing an isoindole fragment can be obtained, are of interest at the synthetic level. Great promise in this direction is opened up by the recently developed method for the synthesis of 1-isoindolones based on the transformation of nitrogen-containing tricyclic compounds 2,3,7,7a-tetrahydro-3a,6-epoxy-2-R-isoindol-1-ones, which can be obtained with high yields from N-alkyl(aryl)-N-furfurylacrylamides by intramolecular [4+2] cycloaddition [5-12]. The epoxyisoindolones can also be obtained by the four-component condensation of furfural and benzylamine or furfurylamine and benzaldehyde with derivatives of maleic and fumaric acids [13].

In the context of the development and study of the applicability limits for the last method we propose a two-stage preparative method for the synthesis of 7-carboxy-2R-isoindol-1-ones **2**, based on the [2+4] cycloaddition of maleic anhydride to N-substituted furfurylamines **1a-j**.

The initial furfurylamines **1a-j** were prepared by reduction of the respective Schiff bases with sodium borohydride in ethanol. Cycloaddition of maleic anhydride to the amines **1a-j** was conducted in benzene at 25°C. The reaction takes place stereoselectively and in most cases with high yields (Table 1). The carboxy-substituted epoxyisoindolones **2a-j** are formed through the initial formation of the N-furfurylamide of maleic acid **2***, which is then transformed through an *exo* transition state into the epoxy derivative **2**.

It is significant that N-acetyl-N-phenylfurfurylamine does not enter into [4+2] cycloaddition with maleic anhydride even after prolonged boiling in xylene, which provides indirect evidence for the described reaction path. It is interesting to note the important role of the substituent R at the nitrogen atom of the furfurylamines **1**. Thus, *Z*-4-(2-furylmethylamino)-4-oxobut-2-enoic acid, which does not undergo an intramolecular Diels–Alder reaction and does not enter into reaction with an excess of maleic anhydride even after heating to 150°C, is formed with a quantitative yield during the reaction of furfurylamine with maleic anhydride.

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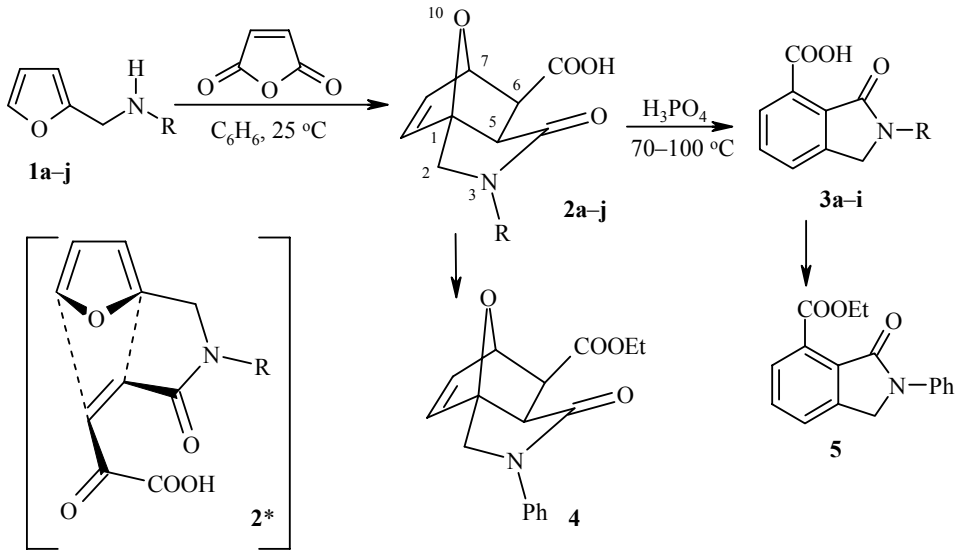

a R = Ph; **b** R = Bn; **c** R = C_6H_4Cl-*m*; **d** R = $C_6H_4NO_2$-*p*; **e** R = $C_6H_4NO_2$-*m*; **f** R = tetrahydrofuryl; **g** R = cyclohexyl; **h** R = methoxyethyl; **i** R = cyclopropyl; **j** R = furfuryl

In spite of existing data on the effective [4+2] cycloaddition of maleic anhydride to furfuryl alcohols [14, 15], we were unable to realize the reaction of maleic anhydride with secondary furfurylamines containing the reactive functional groups –OH or NR_2 in the radical R. During an attempt at cycloaddition to N-(β-hydroxyethyl)-, N-(α-pyridyl)-, and N-(γ-pyridyl)furfurylamines rapid polymerization of the reaction mixtures occurred.

TABLE 1. The Characteristics of Compounds **2a-j**, **3a-i**, **4**, and **5**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1	2	3	4	5	6	7
2a	$C_{15}H_{13}NO_4$	66.43 / 66.42	4.79 / 4.79	5.18 / 5.17	184-185.5*	86
2b	$C_{16}H_{15}NO_4$	67.35 / 67.37	5.27 / 5.26	4.93 / 4.91	164	90
2c	$C_{15}H_{12}NO_4Cl$	58.90 / 58.92	3.95 / 3.93	4.59 / 4.58	179-181*	89
2d	$C_{15}H_{12}N_2O_6$	56.99 / 56.96	7.82 / 7.80	8.84 / 8.86	202-204	74
2e	$C_{15}H_{12}N_2O_6$	56.95 / 56.96	7.84 / 7.80	8.90 / 8.86	205-207	80
2f	$C_{14}H_{17}NO_5$	60.23 / 60.21	6.08 / 6.09	5.03 / 5.01	134-136	37
2g	$C_{15}H_{19}NO_4$	64.97 / 64.98	6.84 / 6.86	5.04 / 5.05	191-192	90
2h	$C_{12}H_{15}NO_5$	56.73 / 56.92	5.87 / 5.93	5.27 / 5.53	127-128.5	92
2i	$C_{12}H_{13}NO_4$	61.29 / 61.28	5.53 / 5.53	5.93 / 5.96	168-171.5	35
2j	$C_{15}H_{13}NO_5$	65.44 / 65.45	4.72 / 4.73	5.05 / 5.09	146-148	95
3a	$C_{15}H_{11}NO_3$	71.13 / 71.15	4.37 / 4.35	5.52 / 5.53	227-230	46
3b	$C_{16}H_{13}NO_3$	71.94 / 71.91	4.85 / 4.87	5.26 / 5.24	177-178.5*	33

TABLE 1 (continued)

1	2	3	4	5	6	7
3c	$C_{15}H_{10}NO_3Cl$	62.62 62.60	3.49 3.48	4.89 4.87	229.5-230*	48
3d	$C_{15}H_{10}N_2O_5$	60.41 60.40	3.35 3.35	9.36 9.39	297 (dec.)*[2]	30
3e	$C_{15}H_{10}N_2O_5$	60.38 60.40	3.36 3.35	9.38 9.39	239-240*[2]	52
3f	$C_{14}H_{15}NO_4$	64.34 64.36	5.78 5.75	5.33 5.36	130-132*	56
3g	$C_{15}H_{17}NO_3$	69.50 69.49	6.56 6.56	5.40 5.40	245-246*	37
3h	$C_{12}H_{13}NO_4$	61.55 61.28	5.51 5.53	5.81 5.92	168.5-170.5	30
3i	$C_{12}H_{11}NO_3$	66.34 66.36	5.04 5.07	6.48 6.45	213-213.5	22
4	$C_{17}H_{17}NO_4$	68.22 68.23	5.60 5.69	4.70 4.68	133-134*[3]	75
5	$C_{17}H_{15}NO_3$	72.59 72.60	5.56 5.34	4.95 4.98	106-107*[4]	86

* Recrystallization from a mixture of *i*-PrOH and DMF.
*[2] DMSO.
*[3] Ethyl acetate.
*[4] from a mixture of hexane and ethyl acetate.

TABLE 2. The Spectral Characteristics of Compounds **2a-5**

Com-pound	Molecular mass		IR, ν, cm^{-1}		
	Found $[M]^+$	Calculated	ν_{NCO}	ν_{COO}	ν_{OH}
2a	271	271	1669	1729	2460
2b	285	285	1659	1729	2485
2c	305, 307	305, 307	1680	1730	—
2d	316	316	1680	1705	2480
2e	316	316	1675	1728	2400
2f	279	279	1680	1720	2500
2g	277	277	1660	1730	2480
2h	253	253	1625	1715	2400
2i	235	235	1630	1710	2460
2j	275	275	1660	1725	2460
3a	253	253	1610	1714	2460
3b	267	267	1600 1583	1713	2300
3c	287, 289	287, 289	1610 1589	1710	2370
3d	298	298	1690	1705	2400
3e	298	298	1615	1711	2410
3f	261	261	1610	1705	2380
3g	259	259	1600	1700	2380
3h	235	235	1615	1720	2300
3i	217	217	1610	1715	2280
4	299	299	1690	1725	—
5	281	281	1640	1715	—

TABLE 3. The ^{1}H NMR Spectra of N-R-4-Oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic Acids **2a-j** and Ethyl N-Phenyl-4-oxo-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (**4**) (TMS)

Com-pound	Chemical shift, δ, ppm*									SSCC (*J*, Hz)				
	COOH	2A-H d	2B-H d	5-H d	6-H d	7-H	8-H	9-H	Others	2A, 2B	5,6	7,8	8,9	Others
2a	12.15 br. s	4.55 d	4.06 d	3.07 d	2.60 d	5.05 d	6.49 dd	6.64 d	7.66 (2H, d); 7.38 (2H, t); 7.14 (1H, t)	11.7	9.1	1.8	5.9	$J_{om} = J_{mp} = 7.3$
2b	—	3.89 d	3.44 d	2.84 d	2.51 d	4.98 d	6.40 dd	6.54 d	7.33-7.21 (2H, m); 4.42 (1H, d); 4.34 (1H, l)	11.7	9.2	1.5	5.7	$J_{AB} = 15.3$ (CH_2Ph)
2c	—	4.52 d	4.06 d	3.07 d	2.59 d	5.02 br. s	6.47 br. d	6.62 d	7.88 (1H, br. s); 7.49 (1H, d); 7.40 (1H, t); 7.17 (1H, d)	11.5	9.2	1.3	5.6	$J_{5'6'} = J_{4'5'} = 8.0$
2d	—	4.58 d	4.18 d	3.15 d	2.67 d	5.03 d	6.48 dd	6.62 d	8.22 (2H, AA'); 7.91 (2H, BB')	11.6	9.1	1.7	5.7	$J_{AB} \sim 9.2$
2e	12.25 br. s	4.64 d	4.19 d	3.14 d	2.65 d	5.07 d	6.51 dd	6.66 d	8.76 (1H, t); 7.96 (2H, dd); 7.69 (1H, t)	11.6	9.2	1.5	5.5	$J_{5'6'} = J_{4'5'} = 8.2$ $J_{2'4'} = J_{2'6'} = 2.1$
2f	9.41 br. s	4.23 d	3.92 d	2.89 d	2.80 d	5.26 c	6.45 d	6.50 d	4.07(1H, dd); 3.95-3.65 (3H, m); 3.16 (1H, dd); 2.10-1.75 (2H, m); 1.70-1.50 (2H, m)	12.5	9.2	0	5.8	$J_{AB} = 14.0$ $J_{A2'} = J_{B2'} = 7.0$ (CH_2CHO)
2g	—	3.84 d	3.82 d	2.86 s		5.32 s	6.48 s		3.85 (1H, m); 1.90-1.60 (10H, m)	11.5	—	—	—	—
2h	—	4.05 d	3.62 d	2.74 d	2.46 d	4.96 d	6.42 dd	6.57 d	3.60-3.40 (3H, m); 3.26 (3H, s); 3.17 (1H, m)	11.6	9.2	1.8	5.8	—
2i	—	3.91 d	3.46 d	3.20 d	2.79 d	4.97 d	6.41 dd	6.53 d	2.67 (1H, m); 0.66 (4H, m)	11.5	9.2	1.3	5.6	$J_{1'2A'} = J_{1'3A'} \sim 5.6$
2j	—	3.96 d	3.78 d	2.80 d	2.50 d	5.35 d	6.50 dd	6.46 d	7.38 (1H, dd); 6.34 (1H, dd); 6.30 (1H, dd); 4.78 (1H, d); 4.30 (d)	12.2	9.0	1.5	5.8	$J_{AB} = 15.6$; $J_{\beta\beta'} = 3.4$ $J_{\alpha\beta'} = 0.8$; $J_{\alpha\beta} = 1.8$ (CH_2furyl)
4	—	4.42 d	4.19 d	2.98 d	2.79 d	5.19 br. s	6.48 br. d	6.58 d	7.58 (2H, d); 7.35 (2H, t); 7.14 (1H, t); 4.27 (m, $\underline{CH_2}CH_3$); 1.32 (t, $CH_2\underline{CH_3}$)	11.4	8.9	~1.0	5.5	$J_{om} = J_{mp} = 7.6$ $J_{CH_2CH_3} = 7.0$

* Solvent: DMSO-d_6 (compounds **2a-i**) and $CDCl_3$ (compounds **2j** and **4**).

TABLE 4. The ^{1}H NMR Spectra of Solutions of 2-R-7-Carboxyisoindolin-1-ones **3a-i** and 7-Ethoxycarbonyl-2-phenylisoindolin-1-one (**5**) (TMS)

Com-pound	Chemical shift,δ, ppm*							SSCC, (*J*, Hz)				
	COOH	3A-H	3B-H	4-H	5-H	6-H	Others	3A,3B	4,5	4,6	5,6	Others
3a	15.53 s	5.04 s		7.85-7.70 m		8.49 dd	7.76 (1H, d); 7.50 (2H, t); 7.34 (2H, t)	—		2.6	6.3	$J_{om} = J_{mp} = 7.5$
3b	—	4.81 s		7.80-7.76 m		8.08 br. d	7.39-7.26 (5H, m); 4.57 (2H, s)	—	—	—	—	—
3c	—	5.18 s		7.88 br. d	7.82 t	7.97 br. d	8.02 (1H, t); 7.80 (1H, dd); 7.51 (1H, t); 7.33 (1H, dd)	—	7.2	0	7.2	$J_{5'6'} = J_{5'4'} = 7.9$; $J_{2'6'} = J_{2'4'} = 1.3$
3d	—	5.09 s		7.70-7.60 m			8.27 (2H) and 8.12 (2H, AA'BB')	—	—	—	—	$J_{AB} \sim 9.1$
3e	—	5.25 s		7.91 d	7.85 t	7.99 d	8.83 (1H, br. s); 8.23 (1H, dd); 8.09 (1H, dd); 7.78 (1H, t)	—	7.3	0	7.3	$J_{5'6'} = J_{5'4'} = 8.2$; $J_{4'6'} = 1.3$
3f	15.74 br. s	4.83 d	4.64 d	7.65 d	7.69 t	8.38 d	4.16 (1H, dq); 3.97 (1H, dd); 3.87 (1H, t); 3.77 (1H, dd); 3.55 (1H, dd); 2.10 (1H, dd); 1.93 (2H, п); 1.63 (1H, dd. d)	18.5	7.2	0	7.2	—
3g	15.94 br. s	4.69 s		7.88 d	7.79 t	8.16 d	4.08 (1H, m); 1.93-1.18 (10H, m)	—	7.4	0	7.4	—
3h	—	4.76 s		7.91 dd	7.81 t	8.16 dd	3.82 (2H, t); 3.64 (2H, t); 3.29 (3H, s)	—	7.6	1.4	7.6	—
3i	—	4.63 s		7.86 br. d	7.79 t	8.15 br. d	3.16-3.03 (1H, m); 1.00-0.85 (4H, m)	—	7.3	0	7.3	—
5	—	4.83 s		7.60 br. s			7.83 (2H, d); 7.40 (2H, t); 7.16 (1H, t); 4.50 (m, $\underline{CH_2}CH_3$); 1.43 (t, $CH_2\underline{CH_3}$)	—	—	—	—	$J_{om} = J_{mp} = 7.6$; $J_{CH_2CH_3} = 7.2$

* Solvent: DMSO-d_6 (compounds **3b-i**) and $CDCl_3$ (compounds **3a** and **5**).

To convert the epoxy derivatives **2a-j** into the 7-carboxyphthalimidines **3a-i** we used hydrochloric and sulfuric acids at various concentrations, 85% phosphoric acid, and boron trifluoride etherate in boiling dioxane. The largest yields of compounds **3** were obtained with $BF_3 \cdot Et_2O$, but from the practical standpoint it is better to use 85% phosphoric acid in the range of 70-100°C. In spite of the fact that the yield of the desired products here is reduced by 10-15% the procedure for the synthesis and the isolation of the isoindolones **3** is greatly simplified.

It was not possible to select conditions for the aromatization of the N-furfuryl-substituted epoxide **2j**. During esterification of the acids **2a** and **3a** the corresponding monoesters **4** and **5** were obtained.

The mass spectra of compounds **2** and **3** (Tables 1 and 2) contain low-intensity peaks of molecular ions, corresponding to their molecular formulas. The readily occurring elimination of a CO_2 molecule and retrodiene dissociation (in the case of the adducts **2**) are the reason for the insufficient reliability of this method of obtaining evidence for the structure of the synthesized substances.

In the IR spectra of the carboxylic acids **2a-j** and **3a-i** there are characteristic bands for the stretching vibrations of the amide and carboxyl groups in the regions of 1610-1690 and 1705-1730 cm^{-1} respectively, and there is also a broad band for the associated hydroxy in the region of 2280-2485 cm^{-1}. In the IR spectra of the esters **4** and **5** the band of the ester group appears at 1715-1725 cm^{-1}.

The ^1H NMR spectra of compounds **2a-j** (Table 3) contain three characteristic signals for the interacting protons 7-H, 8-H, and 9-H with chemical shifts of 4.96-5.35, 6.40-6.51, and 6.46-6.66 ppm respectively and spin–spin coupling constants $^3J_{78}$ = 1.3-1.8 and $^3J_{89}$ = 5.5-5.9 Hz. The absence of the $^3J_{67\text{-}exo}$ spin–spin coupling constant in the bicyclooxaheptene fragment of the molecule indicates unambiguously the *endo* arrangement of the 5-H and 6-H protons (J_{56} = 9.0-9.3 Hz) and the *exo* arrangement of the carboxyl and amide substituents. The protons of the 2-CH_2 group in compounds (**2a-j**) are chemically nonequivalent and are observed in the spectrum in the form of an AB system. Conversely, in the ^1H NMR spectra of compounds **3a-e**,**g-i** the signals of the 3-CH_2 protons are equivalent and are observed in the form of a singlet at 4.63-5.25 ppm. Only in the case of the magnetically anisotropic tetrahydrofuryl substituent R do these protons become nonequivalent and appear in the form of an AB system (Table 4).

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 spectrometer in tablets with potassium bromide. The mass spectra were recorded on an HP MS 5988 mass spectrometer with direct injection of the sample into the ion source with ionizing potential 70 eV. The ^1H NMR spectra were recorded in deuterochloroform and DMSO-d_6 solutions on Bruker WP-200 (200 MHz) or Bruker WH-400 (400 MHz) instruments with TMS as internal standard. Silufol UV-254 plates were used for thin-layer chromatography (development with iodine vapor).

3-R-4-Oxo-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic Acids (2a-j). A mixture of maleic anhydride (0.1 mol) and N-R-furfurylamine **1a-j** (0.1 mol) in benzene (100 ml) was stirred at 25°C for 2-3 days. The precipitate was filtered off, washed with benzene, and dried at 90°C to constant weight. Compounds **2a-j** were obtained in the form of finely crystalline powders. The spectral data and physicochemical characteristics of the tricyclic compounds **2a-j** are given in Tables 1-3.

2-R-Carboxyisoindolin-1-ones (3a-i). The epoxyisoindolinones **2a-i** (0.01 mole) were heated at 70-100°C for 1 h in 85% phosphoric acid (40 ml). The reaction mixture was cooled and poured into water. The crystals that separated were filtered off, washed with water to a neutral reaction in the wash water, dried, and recrystallized from a mixture of isopropyl alcohol and DMF. The spectral data and physicochemical characteristics of the isoindolones **3a-i** are given in Tables 1-3.

Ethyl 4-Oxo-3-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylate (4) and 7-Ethoxycarbonyl-2-phenylisoindolin-1-one (5). To a suspension of compound **2a** (or **3a**) (0.01 mol) in ethanol (50 ml) we added concentrated hydrochloric acid (1 ml). The mixture was boiled for 10-12 h (monitored by TLC). The reaction mixture was poured into water and extracted with ether (3 × 50 ml), and the extract was dried with magnesium sulfate. The residue after distillation of the ether was recrystallized from ethyl acetate. The esters **4** and **5** were obtained in the form of white crystals (Tables 1-4).

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