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CYCLOADDITION OF FURFURYLAMINES TO MALEIC ANHYDRIDE AND ITS SUBSTITUTED DERIVATIVES

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The regio- and stereoselectivity of the [4+2] cycloaddition of maleic, citraconic, dichloromaleic, and dibromomaleic anhydrides to difurfuryl amines and secondary furfurylamines were studied. N-Furfuryl-, N-phenyl-, and N-benzylhexahydrooxoepoxyisoindole-7-carboxylic acids were synthesized. An approach was developed for obtaining hexahydroepoxyoxoisoindole-7-carboxylic acid unsubstituted at the nitrogen atom. Aromatization of the oxabicycloheptene fragment of the dihaloepoxyiso-indolonecarboxylic acids gave a series of 7-carboxy-2-R-isoindol-1-ones.

Keywords: furfurylamines, isoindolones, maleic anhydride, [4+2] cycloaddition.

Functionally substituted epoxyisoindolones hold interest for use in organic synthesis. Pseudo-sugars annelated with azaheterocycles [1-3], and various condensed heterocyclic compounds containing an isoindole fragment may be obtained on the basis of these compounds [4-10]. A recently developed method for the synthesis of isoindol-1-ones holds considerable promise in this regard. This method is based on the acylation of *N*-aryl- or *N*-alkylfurfurylamines by unsaturated acid derivatives with subsequent intramolecular [4+2] cycloaddition of the resultant unsaturated amides [11-19].

The development of this approach is an elaboration of the two-step preparative method for the synthesis of 7-carboxy-2-R-isoindol-1-ones [20] based on [4+2] cycloaddition of maleic anhydride to *N*-substituted furfurylamines. We studied the scope of this reaction and showed the effect of the substituent at the furfuryl-amine nitrogen atom on the cycloaddition. Conditions were found for the aromatization of the oxabicyclo-heptene fragment to give 7-carboxyphthalimidines [21].

In the present work, we have studied the regio- and stereoselectivity of the cycloaddition of maleic, citraconic, dibromomaleic, and dichloromaleic anhydrides to difurfurylamines as well as to phenyl- and benzyl-furfurylamines. An attempt was made to evaluate the effect of substituents in the oxabicycloheptene fragment on the capacity of the Diels-Alder adducts to undergo aromatization.

Starting furfurylamines **1a-h** were obtained as light, mobile oils by the reduction of the corresponding Schiff bases using sodium borohydride in ethanol.

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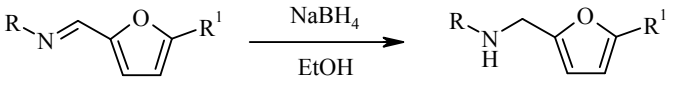
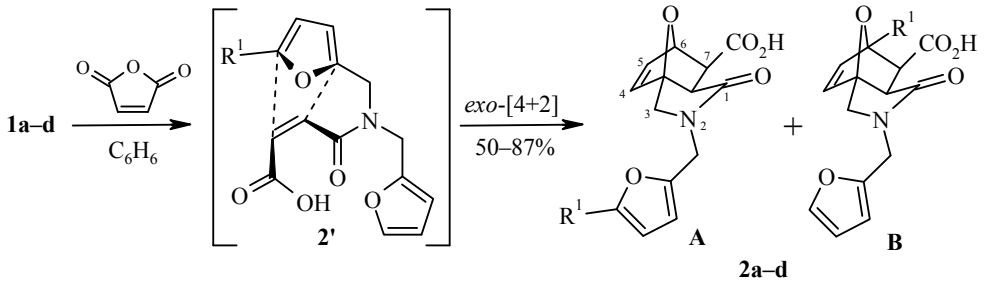


1a–h

a-d R = furfuryl, **e,f** R = Ph, **g,h** R = Bn;
a,e,g, R^1 = H, **b,f,h** R^1 = Me, **c** R^1 = Br, **d** R^1 = I

Difurfurylamines **1a-d** readily undergo cycloaddition with maleic anhydride at room temperature to give a mixture of isomeric *N*-furfurylisoindolonecarboxylic acids **2a-d**. The addition takes place through the intermediate formation of the maleic acid furfurylamide **2'** and subsequent *exo*-[4+2] cycloaddition of the unsaturated fragment to a furan ring [20].



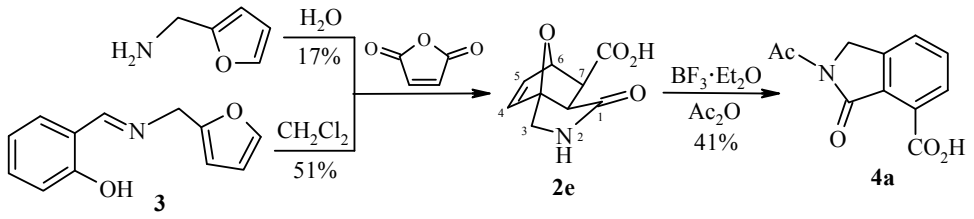
a R^1 = H, **b** R^1 = Me, **c** R^1 = Br, **d** R^1 = I

The cycloaddition to furfurylamines **1b-d** at room temperature proceeds nonselectively at both furan fragments to give a mixture of isomeric *N*-furfuryloxoepoxyisoindolonecarboxylic acids **2b-dA** and **2b-dB**. In the case of 5-methyl- and 5-bromofurylamines **1b,c**, isomers **2b,cB** with substituent R^1 in the oxabicycloheptene fragment predominate in the product mixture, while isomer **2dA** is the major component of the product mixture in the case of iodine derivative **1d**. In the case of difurfurylamine **1b** (R^1 = Me), we showed that lowering the reaction temperature from 25°C to 0-5°C slightly increases the regioselectivity (the fraction of the isomer **2Bb** increases from 1:2.3 to 1:3). Isomer **2bB** is probably the kinetic reaction product (the 5-methylfuran ring is a better diene than its analog lacking a substituent at C-5), while isomer **2bA** is the thermodynamic product (see below). The cycloaddition of maleic anhydride to amines **1a-d** in benzene at reflux proceeds both stereo- and regioselectively. In the case of compounds **1c,d**, the maleimide fragment undergoes cycloaddition to the halofuran fragment to give isomers **2c,dB**, while, in the case of methylfurfurylamine **1b**, the reaction proceeds at the unsubstituted furan fragment to give acid **2bA**.

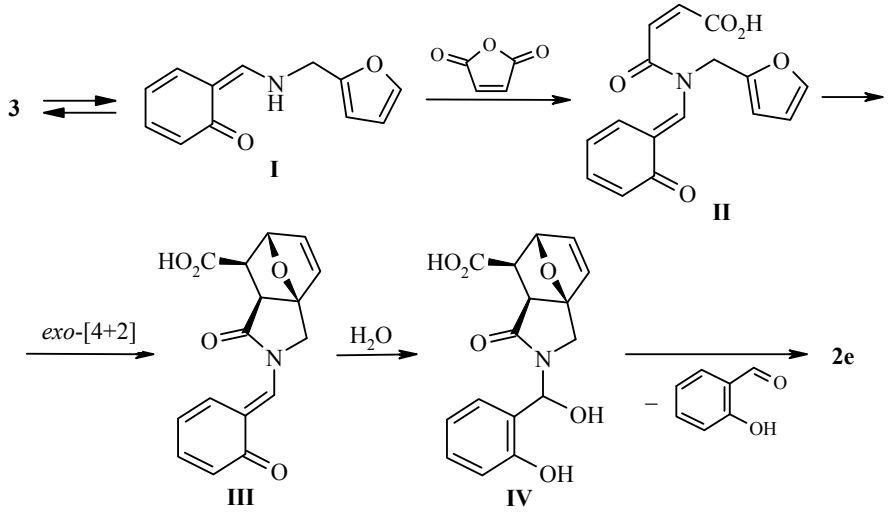
The ratio of isomers **A** and **B** was established by measuring the integral intensities of the signals for H-4, H-5, and H-6 protons in the ^{1}H NMR spectra of the air-dried reaction mixtures (the crystalline adducts precipitated during the reaction were filtered off and washed with ether). The ^{1}H NMR spectra of products **2a-d** show three characteristic signals from coupled protons H-4, H-5, and H-6 with chemical shifts 6.48-6.55, 6.41-6.74, and 4.98-4.99 ppm, respectively, and coupling constants $^3J_{5,6}$ = 1.5-1.7 and $^3J_{4,5}$ = 5.6-5.7 Hz. The lack of a $^3J_{6,7}$ coupling constant in the oxabicycloheptene fragment unequivocally indicates *endo* arrangement of H-7 and H-7a protons ($J_{7,7a}$ = 8.7-9.3 Hz) and, thus, *exo* orientation of the carboxyl and amide substituents. The lack of the characteristic signal for H-6 proton and coupling constant $^3J_{5,6}$ indicate formation of acids **2** as the **B** isomer. The protons of the 3-CH_2 group in isoindolonecarboxylic acids **2a-d** are chemically nonequivalent and appear as an AB system with coupling constant $^2J_{A,B}$ = 11.2-11.8 Hz.

There is no description in the literature of methods of synthesis of epoxyisoindolonecarboxylic acids lacking substituents at the nitrogen atom. The presence of a secondary nitrogen atom opens a broad range of possibilities for modifying such isoindoles at the amide group. Previous attempts to synthesize such compounds by the cycloaddition of maleic anhydride to furfurylamine in various solvents proved unsuccessful [22]. Only acid **2e** was obtained in 17% yield upon heating at reflux in water for 5 h with an equimolar amount of maleic

anhydride. An approach based on the reaction of salicylidenefurfurylamine **3** with maleic anhydride in dichloromethane proved more convenient. In this case, elimination of salicylaldehyde leads to tricyclic product **2e** in 51% yield.



The mechanism of this unusual reaction, apparently, involves nucleophilic attack of the secondary nitrogen atom of tautomeric form **I** of Schiff base **3** at the carbonyl group of maleic anhydride. A subsequent intramolecular Diels-Alder *exo* reaction in resultant amide **II** leads to tricyclic system **III**. The addition of water to compound **III** is accompanied by elimination of salicylaldehyde and finalize the formation of adduct **2e**.



This reaction, although proceeding under mild conditions (25°C), requires prolonged maintenance (3-5 days). This prolonged reaction time is probably necessary for completion of the hydrolysis of quinoid species **III** by atmospheric moisture. Heating has hardly any effect on the reaction rate, while the addition of water to the reaction mixture, likely, leads to hydrolysis of starting azomethine **3**.

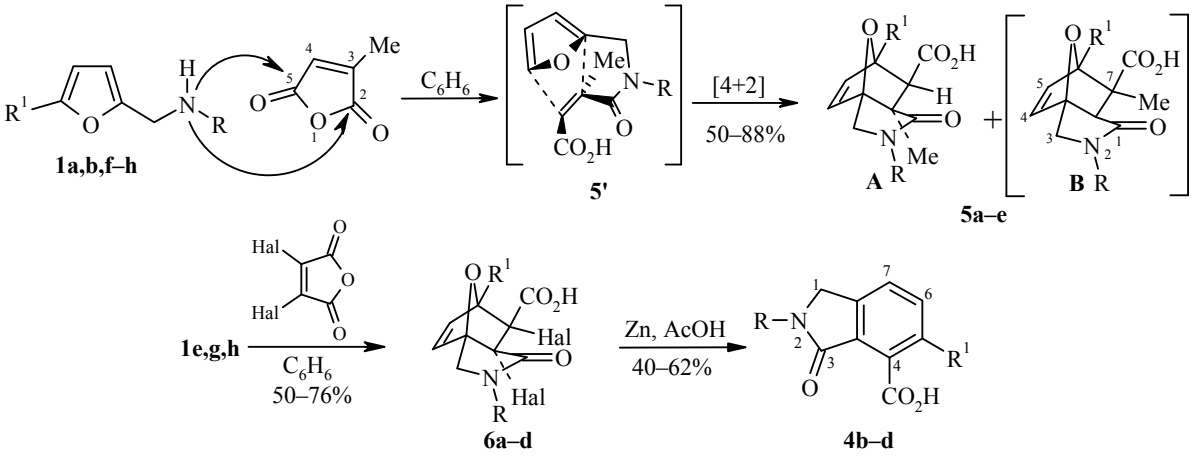
Citraconic anhydride also undergoes cycloaddition with secondary furfurylamines **1a,b,f-h**. Formation of epoxyisoindolonecarboxylic acids **5a-eA** is observed upon heating in benzene at reflux for 4 h.

We might have expected that the reaction of furfurylamines **1a,b,f-h** with citraconic anhydride would lead to two regioisomeric acids **A** and **B** with geminal and vicinal arrangement of the methyl and carboxyl groups. However, only carbonyl carbon C-2 undergoes aminolysis at 80°C such that the *N*-furfurylamide of citraconic acid **5'** is formed, which converts into adducts **5a-eA** with vicinal arrangement of the methyl and carboxyl groups through the *exo* transition state.

In the case of isoindolones **5aA** (R = 5-furfuryl) and **5eA** (R = Bn), the position of the methyl group at C-7a is unequivocally indicated by a combination of NMR methods, including two-dimensional ^{1}H-^{13}C NMR, NOE, HSQC, and HMBC spectra. The most complete information is obtained by the HMBC method, which permits a reliable determination of the hydrocarbon skeleton using the strong cross peaks corresponding to coupling $^{3}J_{Me,C-1}$, $^{3}J_{Me,C-3a}$, and $^{3}J_{H-3,C-7a}$. In our view, measurement of the NOE in samples of these compounds

used for the same purpose by Murali et al. [15, 17] does not provide sufficiently reliable structural information due to the low intensity of the H-7/Me-7a (H-7a/Me-7) cross peaks.

Thus, the position of the *endo*-7a-methyl group in the bicycloheptene fragment in adducts **5A** is in accord with the data of Murali et al. [15, 17] but differs from the corresponding position in the adducts obtained from the cycloaddition of methylmaleic anhydride to 2-furyl heterocycles described in our previous work [6, 23].



1a,**b**, **5a** R = furfuryl; **1e**,**f**, **4b**, **5c**, **6a**,**d** R = Ph; **1g**,**h**, **4c**,**d**, **5d**,**e**, **6b**,**c** R = Bn;
5b R = 5-methylfurfuryl; **1a**,**e**,**g**, **4b**,**c**, **5a**,**b**,**d**, **6a**,**b**,**d** R^1 = H; **1f**,**h**, **4d**, **5c**,**e**, **6c** R^1 = Me;
6a–c Hal = Cl; **6d** Hal = Br

TABLE 1. Physicochemical Characteristics of Compounds **2a-e, 4a,d, 5a-c**, and **6a-d**

Compound	Empirical formula	Found, % / Calculated, %			Mp, ºC
		C	H	N	
2a	$C_{14}H_{13}NO_5$	61.38 / 61.09	4.50 / 4.76	5.64 / 5.09	150-151
2bA	$C_{15}H_{15}NO_5$	62.44 / 62.28	5.07 / 5.23	4.59 / 4.84	106-108
2cB	$C_{14}H_{12}BrNO_5$	47.13 / 47.48	3.56 / 3.42	4.22 / 3.95	>209 (decomp.)
2dB	$C_{14}H_{12}INO_5$	42.13 / 41.92	2.67 / 3.02	3.15 / 3.49	>205 (decomp.)
2e	$C_9H_9NO_4$	55.72 / 55.39	4.47 / 4.65	8.11 / 7.18	152-154
4a	$C_{11}H_9NO_4$	59.91 / 60.27	4.49 / 4.14	6.53 / 6.39	188-190 (decomp.)
4d	$C_{17}H_{15}NO_3$	72.81 / 72.58	5.49 / 5.37	5.13 / 4.98	153-154 (decomp.)
5a	$C_{15}H_{15}NO_5$	62.42 / 62.28	5.68 / 5.23	4.35 / 4.84	106-107
5b	$C_{16}H_{17}NO_5$	63.11 / 63.36	5.33 / 5.65	5.82 / 4.62	145-146
5c	$C_{17}H_{17}NO_4$	68.01 / 68.21	5.65 / 5.72	4.16 / 4.68	133-134
6a	$C_{15}H_{11}Cl_2NO_4$	52.53 / 52.96	3.19 / 3.26	4.27 / 4.12	160-161 (decomp.)
6b	$C_{16}H_{13}Cl_2NO_4$	54.42 / 54.26	3.54 / 3.70	4.26 / 3.95	149-150 (decomp.)
6c	$C_{17}H_{15}Cl_2NO_4$	55.72 / 55.45	4.37 / 4.11	3.65 / 3.80	131-132 (decomp.)
6d	$C_{15}H_{11}Br_2NO_4$	42.33 / 41.99	2.13 / 2.58	3.48 / 3.26	175-176

TABLE 2. IR and ^{1}H NMR Spectra of Compounds **2a-e**, **4a,d**, **5a-c**, and **6a-d**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
2a	1663 (NCO), 1741 (CO_2H)	2.52 (1H, d, *J* = 9.3, H-7a); 2.79 (1H, d, *J* = 9.3, H-7); 3.58 (1H, d, *J* = 11.2) and 3.94 (1H, d, *J* = 11.2, 3-CH_2); 4.30 (1H, d, *J* = 15.6) and 4.52 (1H, d, *J* = 15.6, 2-CH_2); 4.99 (1H, d, *J* = 1.5, H-6); 6.31 (1H, br. d, *J* = 3.2, H-3'); 6.39 (1H, dd, *J* = 1.9, *J* = 3.2, H-4'); 6.41 (1H, dd, *J* = 1.5, *J* = 5.6, H-5); 6.55 (1H, d, *J* = 5.6, H-4); 7.56 (1H, br. d, *J* = 1.9, H-5'); 12.11 (1H, br. s, CO_2H)
2bA	1675 (NCO), 1744 (CO_2H)	2.22 (3H, s, CH_3); 2.52 (1H, d, *J* = 9.2, H-7a); 2.79 (1H, d, *J* = 9.2, H-7); 3.56 (1H, d, *J* = 11.5) and 3.94 (1H, d, *J* = 11.5, 3-CH_2); 4.20 (1H, d, *J* = 15.6) and 4.45 (1H, d, *J* = 15.6, 2-CH_2); 4.97 (1H, d, *J* = 1.7, H-6); 5.99 (1H, dq, *J* = 0.7, *J* = 3.0, H-4'); 6.18 (1H, br. d, *J* = 3.0, H-3'); 6.41 (1H, dd, *J* = 1.7, *J* = 5.7, H-5); 6.55 (1H, d, *J* = 5.7, H-4)
2cB	1675 (NCO), 1750 (CO_2H)	2.97 (1H, d, *J* = 8.7, H-7a); 3.01 (1H, d, *J* = 8.7, H-7); 3.64 (1H, d, *J* = 11.8) and 3.94 (1H, d, *J* = 11.8, 3-CH_2); 4.32 (1H, d, *J* = 15.6) and 4.50 (1H, d, *J* = 15.6, 2-CH_2); 6.35 (1H, dd, *J* = 0.9, *J* = 3.1, H-3'); 6.41 (1H, dd, *J* = 1.9, *J* = 3.1, H-4'); 6.48 (1H, d, *J* = 5.6, H-4); 6.74 (1H, d, *J* = 5.6, H-5); 7.59 (1H, dd, *J* = 0.9, *J* = 1.9, H-5')
2dB	1670 (NCO), 1745 (CO_2H)	2.88 (1H, d, *J* = 8.8, H-7a); 2.93 (1H, d, *J* = 8.8, H-7); 3.62 (1H, d, *J* = 11.8) and 3.92 (1H, d, *J* = 11.8, 3-CH_2); 4.30 (1H, d, *J* = 16.0) and 4.50 (1H, d, *J* = 16.0, 2-CH_2); 6.35 (1H, dd, *J* = 0.8, *J* = 3.2, H-3'); 6.41 (1H, dd, *J* = 1.8, *J* = 3.2, H-4'); 6.54 (1H, d, *J* = 5.6, H-4); 6.55 (1H, d, *J* = 5.6, H-5); 7.58 (1H, dd, *J* = 0.8, *J* = 1.8, H-5')
2e	1634 (NCO), 1733 (CO_2H), 3355 (NH)	2.43 (1H, d, *J* = 9.3, H-7a); 2.67 (1H, d, *J* = 9.3, H-7); 3.47 (1H, dd, *J* = 11.7, *J* = 1.4) and 3.85 (1H, d, *J* = 11.7, 3-CH_2); 4.97 (1H, d, *J* = 1.7, H-6); 6.42 (1H, dd, *J* = 5.7, *J* = 1.7, H-5); 6.57 (1H, d, *J* = 5.7, H-4); 7.64 (1H, s, NH); 12.15 (1H, br. s, CO_2H)
4a	1640 (NCO), 1722 (CO_2H)	2.74 (3H, s, CH_3); 4.96 (2H, s, 1-CH_2); 7.79 (1H, br. d, *J* = 7.9, H-7); 7.89 (1H, t, *J* = 7.9, H-6); 8.54 (1H, br. d, *J* = 7.9, H-5); 14.31 (1H, s, CO_2H)
4d	1602 (NCO), 1712 (CO_2H)	2.33 (3H, s, 5-CH_3); 4.33 (2H, s, 1-CH_2); 4.70 (2H, s, CH_2Ph); 7.26-7.46 (7H, m, H Ar)
5a	1667 (NCO), 1736 (CO_2H)	1.03 (3H, s, 7a-CH_3); 2.06 (1H, s, H-7); 3.53 (1H, d, *J* = 11.8) and 3.82 (1H, d, *J* = 11.8, 3-CH_2); 4.26 (1H, d, *J* = 15.6) and 4.54 (1H, d, *J* = 15.6, 2-CH_2); 4.89 (1H, d, *J* = 1.6, H-6); 6.30 (1H, br. d, *J* = 3.0, H-3'); 6.39 (1H, dd, *J* = 1.9, *J* = 3.0, H-4'); 6.51 (1H, dd, *J* = 1.6, *J* = 5.6, H-5); 6.53 (1H, d, *J* = 5.6, H-4); 7.56 (1H, br. d, *J* = 1.9, H-5'); 12.05 (1H, br. s, CO_2H)
5b	1644 (NCO), 1722 (CO_2H)	0.99 (3H, s, 7a-CH_3); 2.02 (1H, s, H-7); 2.19 (3H, d, *J* = 0.8, 5'-CH_3); 3.49 (1H, d, *J* = 11.7) and 3.77 (1H, d, *J* = 11.7, 3-CH_2); 4.13 (1H, d, *J* = 15.6) and 4.45 (1H, d, *J* = 15.6, 2-CH_2); 4.84 (1H, d, *J* = 1.6, H-6); 5.94 (1H, dq, *J* = 0.8, *J* = 3.0, H-4'); 6.11 (1H, d, *J* = 3.0, H-3'); 6.47 (1H, dd, *J* = 1.6, *J* = 5.7, H-5); 6.50 (1H, d, *J* = 5.7, H-4)
5c	1712 (NCO), 1750 (CO_2H)	1.12 (3H, s, 7a-CH_3); 1.52 (3H, s, 6-CH_3); 2.21 (1H, s, H-7); 4.02 (1H, d, *J* = 11.8) and 4.45 (1H, d, *J* = 11.8, 3-CH_2); 6.40 (1H, d, *J* = 5.6, H-4); 6.66 (1H, d, *J* = 5.6, H-5); 7.14 (1H, br. t, *J* = 7.5, H-4'); 7.38 (2H, br. t, *J* = 7.5, H-3',5'); 7.65 (2H, br. d, *J* = 7.5, H-2',6')
6a	1701 (NCO), 1746 (CO_2H)	4.26 (1H, d, *J* = 12.5) and 4.66 (1H, d, *J* = 12.5, 3-CH_2); 5.58 (1H, d, *J* = 1.9, H-6); 6.77 (1H, dd, *J* = 1.9, *J* = 5.6, H-5); 6.85 (1H, d, *J* = 5.6, H-4); 7.24 (1H, br. t, *J* = 7.5, H-4'); 7.44 (2H, br. t, *J* = 7.5, H-3',5'); 7.65 (2H, br. d, *J* = 7.5, H-2',6')
6b	1674 (NCO), 1746 (CO_2H)	3.60 (1H, d, *J* = 12.5) and 3.97 (1H, d, *J* = 12.5, 3-CH_2); 4.44 (1H, d, *J* = 15.6) and 4.52 (1H, d, *J* = 15.6, 2-CH_2); 5.51 (1H, d, *J* = 1.9, H-6); 6.69 (1H, dd, *J* = 1.9, *J* = 5.6, H-5); 6.75 (1H, d, *J* = 5.6, H-4); 7.24-7.37 (5H, m, H Ph)
6c	1666 (NCO), 1751 (CO_2H)	1.57 (3H, s, 6-CH_3); 3.59 (1H, d, *J* = 12.5) and 3.90 (1H, d, *J* = 12.5, 3-CH_2); 4.41 (1H, d, *J* = 14.8) and 4.49 (1H, d, *J* = 14.8, 2-CH_2); 6.48 (1H, d, *J* = 5.5, H-5); 6.70 (1H, d, *J* = 5.5, H-4); 7.24 (2H, br. d, *J* = 7.5, H-2',6'); 7.28 (1H, br. t, *J* = 7.5, H-4'); 7.33 (2H, br. t, *J* = 7.5, H-3',5')
6d	1700 (NCO), 1739 (CO_2H)	4.22 (1H, d, *J* = 12.5) and 4.58 (1H, d, *J* = 12.5, 3-CH_2); 5.56 (1H, d, *J* = 1.9, H-6); 6.73 (1H, dd, *J* = 1.9, *J* = 5.6, H-5); 6.77 (1H, d, *J* = 5.6, H-4); 7.21 (1H, t, *J* = 7.5, H-4'); 7.42 (2H, br. t, *J* = 7.5, H-3',5'); 7.63 (2H, br. d, *J* = 7.5, H-2',6')

Dibromo- and dichloromaleic anhydrides [24, 25] react with *N*-furfurylamines **1e,g,h** even at room temperature to give *exo* adducts **6a-d** in good yields.

All adducts **2a-e**, **5a-e**, and **6a-d** are colorless crystalline compounds with poor solubility in most organic solvents. The IR spectra of these compounds have characteristic stretching vibrational bands for the amide and carboxyl groups at 1634-1712 and 1722-1751 cm^{-1}, respectively. The mass spectra of **2a-e**, **5a-c**, and **6a-d** show weak molecular ion peaks corresponding to their chemical formulas.

The presence of an acidophobic furan fragment in acids **2a-d**, free NH group in compound **2e**, and methyl group or halogen atoms in the oxabicycloheptene fragment in acids **5** and **6** significantly hinders aromatization of the epoxy-containing ring or even makes this process impossible. Attempts to effect aromatization of the 7-oxa-bicyclo[2.2.1]heptene fragment by the action of strong mineral acids such as HCl, H_3PO_4, and H_2SO_4 at various concentrations [20] were unsuccessful. Acid **2e** is aromatized at room temperature by boron trifluoride etherate in acetic anhydride to give isoindolone **4a**. Aromatization of dihaloacids **6a-c** was carried out using zinc in acetic acid. Acids **4b-d** were obtained in satisfactory yields.

TABLE 3. ^{13}C NMR Spectra of Compounds **2a-e**, **4a,d**, **5a-c**, and **6a-d**

Compound	Chemical shifts, δ, ppm
2a	38.8 (CH_2); 44.5 (C-7a); 47.8 (C-3); 49.9 (C-7); 81.1 (C-6); 88.2 (C-3a); 107.8 (C-4'); 110.5 (C-3'); 135.5 (C-5); 136.6 (C-4); 142.6 (C-5'); 150.0 (C-2'); 170.1 (C-1); 172.7 (CO_2H)
2bA	13.3 (CH_3); 38.9 (CH_2); 44.6 (C-7a); 47.8 (C-3); 50.1 (C-7); 81.2 (C-6); 88.3 (C-3a); 106.5 (C-4'); 108.8 (C-3'); 135.6 (C-5); 136.7 (C-4); 148.2 (C-5'); 151.3 (C-2'); 170.1 (C-1); 172.8 (CO_2H)
2cB	38.8 (CH_2); 47.7 (C-3); 51.1 (C-7a); 53.0 (C-7); 87.3 (C-3a); 90.5 (C-6); 108.8 (C-4'); 110.6 (C-3'); 138.0 (C-5); 139.8 (C-4); 142.7 (C-5'); 149.8 (C-2'); 169.2 (C-1); 169.6 (CO_2H)
2dB	38.8 (CH_2); 47.3 (C-3); 52.0 (C-7a); 52.8 (C-7); 87.9 (C-3a); 88.3 (C-6); 108.0 (C-4'); 110.5 (C-3'); 135.5 (C-5); 137.2 (C-4); 142.7 (C-5'); 149.8 (C-2'); 169.3 (C-1); 170.4 (CO_2H)
2e	43.2 (C-3); 44.5 (C-7); 49.3 (C-7a); 81.2 (C-6); 91.3 (C-3a); 135.9 (C-5); 136.6 (C-4); 173.1 (C-1); 173.2 (CO_2H)
4a	25.3 ($CO\underline{C}H_3$); 49.0 (C-1); 127.8 (C-7); 128.4 (C-6); 130.8 (C-5); 134.8 (C-4); 135.2 (C-3a); 142.5 (C-7a); 164.1 (CO); 170.4 (CO_2H); 171.1 (C-3)
4d	18.1 (CH_3); 45.4 (CH_2); 48.8 (C-1); 123.5 (C-7); 127.3 (C-4'); 127.6 (C-4); 127.7 (C-3',5'); 128.0 (C-5); 128.6 (C-2',6'); 128.8 (C-1); 133.0 (C-6); 137.3 (C-3a); 139.4 (C-7a); 166.1 (C-3); 168.6 (CO_2H)
5a	21.5 (CH_3); 38.9 (CH_2); 46.4 (C-3); 52.6 (C-7); 55.7 (C-7a); 80.7 (C-6); 90.4 (C-3a); 107.8 (C-4'); 110.6 (C-3'); 133.5 (C-5); 137.6 (C-4); 142.7 (C-5'); 150.1 (C-2'); 172.9 (C-1); 173.7 (CO_2H)
5b	13.2 (CH_3); 21.4 (CH_3); 38.9 (CH_2); 46.3 (C-3); 52.5 (C-7); 55.6 (C-7a); 80.6 (C-6); 90.3 (C-3a); 106.4 (C-4'); 108.5 (C-3'); 133.5 (C-5); 137.5 (C-4); 148.2 (C-5'); 151.2 (C-2'); 172.8 (C-1); 173.6 (CO_2H)
5c	15.6 (CH_3); 21.8 (CH_3); 48.1 (C-3); 56.9 (C-7); 60.0 (C-7a); 88.0 (C-6); 88.9 (C-3a); 119.5 (C-2',6'); 123.9 (C-4'); 128.6 (C-3',5'); 134.3 (C-4); 139.6 (C-1'); 140.5 (C-5); 171.6 (C-1); 174.0 (CO_2H)
6a	48.4 (C-3); 72.5 (C-7a); 75.5 (C-7); 85.7 (C-6); 90.5 (C-3a); 120.7 (C-2',6'); 125.9 (C-4'); 129.5 (C-3',5'); 133.9 (C-5); 138.9 (C-1'); 139.6 (C-4); 166.3 (C-1); 168.2 (CO_2H)
6b	46.2 (CH_2); 46.7 (C-3); 71.9 (C-7a); 74.7 (C-7); 85.5 (C-6); 91.5 (C-3a); 127.9 (C-3',5'); 128.1 (C-4'); 129.2 (C-2',6'); 134.3 (C-5); 136.3 (C-1'); 139.2 (C-4); 167.3 (C-1); 168.2 (CO_2H)
6c	14.2 (CH_3), 45.7 (CH_2); 46.7 (C-3); 76.2 (C-7a); 77.7 (C-7); 90.1 (C-6); 93.0 (C-3a); 127.5 (C-3',5'); 128.4 (C-4'); 128.7 (C-2',6'); 134.5 (C-5); 135.8 (C-1'); 141.4 (C-4); 166.4 (C-1); 167.3 (CO_2H)
6d	47.8 (C-3); 65.8 (C-7a); 68.0 (C-7); 85.1 (C-6); 90.2 (C-3a); 120.0 (C-2',6'); 125.1 (C-4'); 128.9 (C-3',5'); 133.1 (C-5); 138.5 (C-1'); 139.7 (C-4); 165.8 (C-1); 167.5 (CO_2H)

TABLE 4. Mass Spectra of Compounds **2a-e**, **4a,d**, **5a-c**, and **6a-d**

Compound	*m/z* (I_{rel}, %)
2a	275 $[M]^+$ (3), 231 (2), 194 (47), 176 (31), 150 (18), 121 (12), 109 (64), 99 (61), 80 (100), 69 (24), 54 (94), 43 (63)
2b	289 $[M]^+$ (22), 208 (87), 194 (54), 164 (13), 150 (21), 110 (100), 96 (83), 80 (92), 67 (13), 55 (70), 43 (40)
2c	353 $[M]^+$ (for ^{79}Br) (3), 274 (27), 254 (19), 228 (17), 194 (70), 176 (76), 159 (52), 148 (29), 131 (47), 109 (38), 96 (72), 80 (100), 67 (26), 53 (88), 43 (65), 32 (34)
2d	401 $[M]^+$ (6), 320 (64), 276 (14), 222 (46), 207 (72), 194 (67), 179 (39), 147 (16), 128 (67), 109 (38), 96 (73), 80 (100), 59 (54), 53 (85), 44 (49)
2e	195 $[M]^+$ (3), 177 (20), 96 (100), 81 (40), 69 (18), 53 (23), 39 (17)
4a	219 $[M]^+$ (5), 191 (11), 175 (92), 145 (13), 133 (100), 104 (42), 89 (14), 76 (37), 59 (47), 43 (78)
5a	289 $[M]^+$ (6), 208 (47), 176 (22), 122 (100), 113 (75), 96 (80), 80 (72), 69 (39), 53 (52), 43 (35)
5b	303 $[M]^+$ (11), 222 (83), 204 (27), 190 (67), 136 (12), 123 (57), 109 (100), 95 (92), 80 (96), 68 (41), 59 (42), 53 (43), 43 (52)
5c	299 $[M]^+$ (12), 254 (21), 187 (100), 143 (11), 106 (36), 95 (96), 77 (24), 68 (30), 51 (21), 41 (56)
6a	340 $[M]^+$ (for ^{35}Cl) (3), 304 (41), 260 (22), 224 (76), 196 (71), 172 (52), 140 (22), 123 (48), 105 (47), 86 (100), 76 (94), 65 (44), 53 (82), 43 (47)
6b	353 $[M]^+$ (for ^{35}Cl) (3), 318 (21), 274 (30), 238 (22), 218 (24), 182 (58), 146 (41), 122 (78), 105 (43), 96 (100), 86 (97), 65 (72), 53 (68), 43 (31)
6c	368 $[M]^+$ (for ^{35}Cl) (3), 332 (11), 276 (13), 252 (21), 232 (14), 196 (82), 160 (40), 122 (79), 110 (69), 91 (100), 77 (43), 65 (67), 52 (87)
6d	427 $[M]^+$ (for ^{79}Br) (2), 348 (4), 303 (7), 255 (13), 223 (24), 195 (28), 172 (34), 143 (16), 130 (81), 104 (49), 80 (100), 65 (22), 53 (74), 43 (67)

EXPERIMENTAL

IR spectra were obtained on an IR Fourier spectrometer Infralum FT-801 using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker WH-400 spectrometer at 400 MHz and JEOL JNM-ECA600 spectrometer at 600 MHz at 26°C in ~3% DMSO-d_6 solutions using the residual solvent signal at 2.49 ppm as internal standard. A Bruker AMX-400 spectrometer at 100 MHz was used to record the ^{13}C NMR spectra with the central signal of the DMSO-d_6 multiplet at 39.96 ppm as the standard. The mass spectra were recorded on a Thermo Trace DSQ spectrometer with direct sample inlet into the ion source. The ionization energy was 70 eV. The melting points of the samples synthesized were determined SMP 30 melting points apparatus and were uncorrected. Sorbfil plates were used for thin-layer chromatography with iodine vapor development. The reaction products were purified by recrystallization from 2-propanol–DMF. The isomer ratio in the reaction products was determined using the ^{1}H NMR spectra as the ratio of integral intensities of monotypic protons. Activated, neutral alumina (50-200 mesh) was used for column chromatography. Reagents from Acros Organics were used without further purification. Freshly distilled solvents were used for the syntheses.

The physicochemical characteristics and elemental analysis data for all the new compounds are given in Table 1, while the ^{1}H NMR spectral data are given in Table 2, the ^{13}C NMR spectral data are given in Table 3, and the mass spectra are given in Table 4.

(3a*S,6*R**,7*S**,7a*R**)-2-(Furylmethyl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (2a), (3a*S**,6*R**,7*S**,7a*R**)-2-[(5-Methyl-2-furyl)methyl]-1-oxo-1,2,5,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (2bA), (3a*S**,6*R**,7*S**,7a*R**)-2-(2-Furylmethyl)-6-methyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisodindole-7-carboxylic Acid (2bB), (3a*S**,6*R**,7*S**,7a*R**)-2-[(5-Bromo-2-furyl)methyl]-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (2cA), (3a*S**,6*S**,7*R**,7a*R**)-6-Bromo-2-(2-furylmethyl)-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (2cB), (3a*S**,6*R**,7*S**,7a*R**)-2-[(5-Iodo-2-furyl)methyl]-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (2dA),**

and (3a*S,6*S**,7*R**,7a*R**)-2-(2-Furylmethyl)-6-iodo-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (2dB) (General Method)**. A. A solution of maleic anhydride (2.24 g, 0.023 mol) in benzene (50 ml) was added to a solution of amine **1b-d** (0.020 mol) in benzene (50 ml) at 20°C, and the mixture was maintained until the end of the reaction as indicated by thin-layer chromatographic monitoring. The precipitate was filtered off and washed with ether (2×15 ml) to give a mixture of isomers **A** and **B** of carboxylic acids **2b-d** as colorless crystals. The yields were 79% for **2b**, 52% for **2c**, and 50% for **2d**. The **A/B** isomer ratio was 30:70 for **2b**, 45:55 for **2c**, and 60:40 for **2c**.

B. A solution of amine **1a-d** (0.020 mol) and maleic anhydride (2.24 g, 0.023 mol) in benzene (100 ml) was heated at reflux for 10 h to give pure carboxylic acids **2a** in 87% yield, **2bA** in 86% yield, **2cB** in 78% yield, and **2dB** in 70% yield as colorless crystals.

(3a*S,6*R**,7*S**,7a*R**)-1-Oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (2e).** A solution of maleic anhydride (15.1 g, 0.154 mol) and salicylidenefurfurylamine **3** (15.5 g, 0.077 mol) in CH_2Cl_2 (100 ml) was stirred for 72 h at 20°C. The fine crystalline powder precipitate was filtered off, washed with CH_2Cl_2, (2×25 ml) and recrystallized from 2-propanol–DMF to give 11.1 g (51%) acid **2e** as colorless crystals.

2-Acetyl-3-oxo-2,3-dihydro-1*H*-isoindole-4-carboxylic Acid (4a). $BF_3 \cdot Et_2O$ (6.6 ml, 0.05 mol) was added to a solution of epoxyisoindolonecarboxylic acid **2e** (10.42 g, 0.05 mol) in freshly distilled acetic anhydride (70 ml). The reaction mixture was stirred for 24 h at 20°C with thin-layer chromatographic monitoring, poured into water (100 ml), and extracted with methylene chloride (3×50 ml). The extract was dried over anhydrous magnesium sulfate. The solvent was distilled off in vacuum. The dark oily residue was purified by column chromatography on a 40×100-cm alumina column using 1:1 ethyl acetate–hexane as the eluent to give 4.60 g (41%) acid **4a** as pale-yellow crystals.

3-Oxo-2-phenyl-2,3-dihydro-1*H*-isoindole-4-carboxylic Acid (4b), 2-Benzyl-3-oxo-2,3-dihydro-1*H*-isoindole-4-carboxylic Acid (4c), and 2-Benzyl-5-methyl-3-oxo-2,3-dihydro-1*H*-isoindole-4-carboxylic Acid (4d) (General Method). Zinc dust (1.1 g, 16.90 mmol) was added to a solution of carboxylic acid **6a-c** (0.28 mmol) in glacial acetic acid (10 ml) and stirred for 2 h at 70°C. The reaction mixture was cooled and water (100 ml) was added. The mixture was neutralized by adding ammonium hydroxide. Unreacted zinc was filtered off. The filtrate was brought to pH 4-5 by adding concentrated hydrochloride acid. The crystalline precipitate was filtered off and washed with ether (2×15 ml). Recrystallization from 2-propanol–DMF gave the corresponding acids as colorless crystals: **4b** in 45% yield, **4c** in 62% yield, and **4d** in 40% yield. The physicochemical characteristics and spectral data for acids **4b,c** were identical to the results reported in our previous work [20].

(3a*S,6*R**,7*S**,7a*R**)-2-(2-Furylmethyl)-7a-methyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (5a), (3a*S**,6*R**,7*S**,7a*R**)-7a-Methyl-2-[(5-methyl-2-furyl)methyl]-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (5b), (3a*S**,6*R**,7*S**,7a*R**)-6,7a-Dimethyl-1-oxo-2-phenyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (5c), (3a*S**,6*R**,7S*,7a*R**)-2-Benzyl-7a-methyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (5d), and (3a*S**,6*R**,7*S**,7a*R**)-2-Benzyl-6,7a-dimethyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (5e) (General Method)**. Corresponding amine **1a,b,f-h** (0.011 mol) and citraconic anhydride (1.1 ml, 0.012 mol) in benzene (30 ml) were heated at reflux for 6 h with thin-layer chromatographic monitoring. The residue after distilling off the solvent was recrystallized from 2-propanol–DMF to give the corresponding acids as colorless crystals: **5a** in 88% yield, **5b** in 50% yield, **5c** in 59% yield, **5d** in 65% yield, and **5e** in 69% yield. The physicochemical characteristics and spectral data for acids **5d,e** were identical to the results obtained by Murali et al. [15, 17].

(3a*R,6*R**,7*R**,7a*S**)-7,7a-Dichloro-1-oxo-2-phenyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (6a), (3a*R**,6*R**,7*R**,7a*S**)-2-Benzyl-7,7a-dichloro-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (6b), (3a*R**,6*R**,7*R**,7a*S**)-2-Benzyl-7,7a-dichloro-6-methyl-1-oxo-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic Acid (6c), and (3a*R**,6*R**,7*R**,7a*S**)-7,7a-Dibromo-1-oxo-2-phenyl-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole-7-carboxylic acid (6d) (General**

Method). A solution of amine **1e,g,h** (0.011 mol) and dichloro- (1.8 g, 0.011 mol) (for **6a-c**) or dibromomaleic anhydride (2.8 g, 0.011 mol) (for **6d**) in benzene (20 ml) was stirred for 72 h at 20°C with monitoring by thin-layer chromatography. The crystalline precipitate was filtered off and washed with ether (2×15 ml). Recrystallization from 2-propanol–DMF gave colorless crystals of the corresponding acids: **6a** in 51% yield, **6b** in 50% yield, **6c** in 55% yield, and **6d** in 76% yield.

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