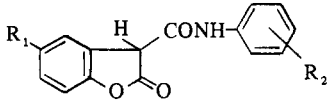


Table I. Physical Properties and Methods of Preparation of 2,3-Dihydro-2-oxobenzofuran-3-carboxanilides



Compd	R ₁	R ₂	Mp, °C	Method of prepn	Yield, %	Solvent of recrystn	Formula ^a	pK _a ^b
1	H	H	179-181	A ^b	30	EtOH	C ₁₅ H ₁₁ NO ₃	3.79
2	H	2-CH ₃	164-165	A	32	C ₆ H ₆	C ₁₆ H ₁₃ NO ₃	3.57
3	H	3-CH ₃	158-159	B ^b	13	C ₆ H ₆	C ₁₆ H ₁₃ NO ₃	
4	H	4-CH ₃	173-174	B	36	EtOH	C ₁₆ H ₁₃ NO ₃	4.00
5	H	2-F	157-158	B	29	C ₆ H ₆ -hexane	C ₁₅ H ₁₀ FNO ₃	3.22
6	H	4-F	175-177	B	25	C ₆ H ₆ -hexane	C ₁₅ H ₁₀ FNO ₃	
7	H	2-Cl	140-142	B	14	C ₆ H ₆ -hexane	C ₁₅ H ₁₀ ClNO ₃	3.00
8	H	3-Cl	183-184	B	15	EtOAc-hexane	C ₁₅ H ₁₀ ClNO ₃	3.36
9	H	4-Cl	184-185	B	13	<i>i</i> -PrOH-H ₂ O	C ₁₅ H ₁₀ ClNO ₃	3.42
10	H	4-Br	199-200	B	29	C ₆ H ₆	C ₁₅ H ₁₀ BrNO ₃	3.47
11	H	2-OCH ₃	142-143	A	37	EtOAc	C ₁₆ H ₁₃ NO ₄	3.57
12	H	4-OCH ₃	204-205	B	32	C ₆ H ₆	C ₁₆ H ₁₃ NO ₄	4.04
13	Cl	H	186-188	C ^b	46	C ₆ H ₆	C ₁₅ H ₁₀ ClNO ₃	
14	Cl	2-CH ₃	196-198	C	33	MeCN	C ₁₆ H ₁₂ ClNO ₃	
15	Cl	3-CH ₃	181-183	C	66	MeCN	C ₁₆ H ₁₂ ClNO ₃	
16	Cl	2-Cl	147-148	C	60	C ₆ H ₆ -hexane	C ₁₅ H ₉ Cl ₂ NO ₃	
17	Cl	4-Cl	222-223	C	25	<i>i</i> -PrOH	C ₁₅ H ₉ Cl ₂ NO ₃	
18	Cl	2-OCH ₃	131-132	C	57	C ₆ H ₆ -hexane	C ₁₆ H ₁₂ ClNO ₄	
19	Cl	4-OCH ₃	208-209	C	69	MeCN	C ₁₆ H ₁₂ ClNO ₄	

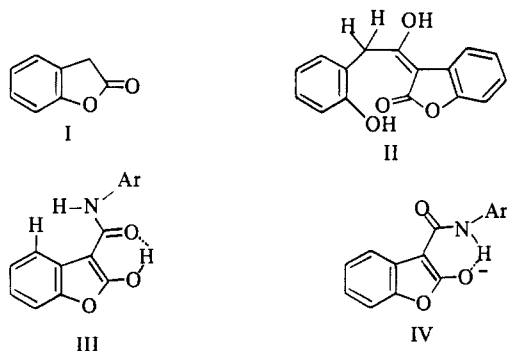
^aAll analyses are within $\pm 0.3\%$ of calcd values. ^bSee Experimental Section.

poured over cold 1 *N* HCl. The resulting ppt was filtered, dried, and recrystd.

Method B. The appropriate isocyanate was added to equimolar amts of Et₃N and lactone in DMF. After stirring for 30-90 min, the reaction mixt was partitioned between Et₂O or EtOAc and aqueous base. The aqueous layer was sepd and acidified with 6 *N* HCl. The resulting ppt was filtered, dried, and recrystd.

Method C. Identical with method B except that the lactone was added to the Et₃N-isocyanate mixt in DMF.

Reaction of I with Diethyl Carbonate. A soln of 5.36 g (0.04 mole) of I in dry THF was added to a cold suspension of 1.6 g (0.04 mole) of a 60% mineral oil dispersion of NaH in THF. Gas was liberated; to the resulting thick suspension there was added, dropwise, 4.72 g (0.04 mole) of diethyl carbonate. After stirring the reaction mixt for 1 hr, during which time room temp was attained, it was dild with 200 ml of H₂O. The aqueous soln was shaken once with Et₂O, sepd, and acidified with 6 *N* HCl. The resulting ppt was filtered and dried to give 4.93 g of II, mp 157.5-159° (lit.⁵ mp 156-157°), nmr (DMSO-*d*₆) δ 4.32 (s, 2 H, CH₂C=O), 10.16 (broad, 2 H, enol and phenol). *Anal.* (C₁₆H₁₂O₄) C, H.



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Substituted Anilides of 3-Monoethyl Ester of 4-Hydroxyisophthalic Acid

R. Spano,* G. Linari, and R. Marri

Istituto Farmaco Biologico Stroder, 50126 Florence, Italy.
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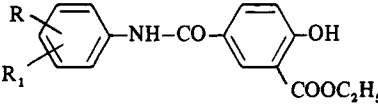
The fact that 4-hydroxyisophthalic acid shows various biological activities, notably analgetic,¹ prompted us to perform the synthesis and some pharmacological evaluation of the title compounds. The standard methods of synthesis are given in the Experimental Section. All the derivatives were tested for analgetic action by the hot plate test² using mice weighing 18-22 g. Their activities are listed in Table I. All the derivatives showed low toxicity in mice (LD₅₀ > 650 mg/kg).

Experimental Section†

General Procedure for the Preparation of the Compounds Described in Table I. The 3-monoethyl ester of 4-hydroxyisophthalic acid³ (0.05 mole) and 50 ml of thionyl chloride were refluxed for 5 hr. The excess thionyl chloride was distilled under reduced pressure and the residue washed twice with anhydrous benzene. The 3-monoethyl ester of 4-hydroxyisophthalic acid chloride so obtained, without further purifications, was dissolved in 50 ml of anhydrous dioxane. This solution was treated with

†All compounds were analyzed for C, H, N, and their melting points were uncorrected.

Table I.

							
No.	R	R ₁	Mp, °C	Recrystallization solvent ^a	Formula	Analgetic activity (mice) ^{b,c}	Probability ^d P ≤
1	H	H	159-160	B	C ₁₆ H ₁₅ NO ₄	37.1	<0.001
2	2Cl	H	154-155	A	C ₁₆ H ₁₄ ClNO ₄	52.5	<0.001
3	3Cl	H	143-144	A	C ₁₆ H ₁₄ ClNO ₄	56.4	<0.001
4	4Cl	H	195-196	A	C ₁₆ H ₁₄ ClNO ₄	32	<0.005
5	2Cl	3Cl	157-158	C	C ₁₆ H ₁₃ Cl ₂ NO ₄	64.1	<0.001
6	2Cl	4Cl	164-165	C	C ₁₆ H ₁₃ Cl ₂ NO ₄	74.3	<0.001
7	2Cl	5Cl	203-204	C	C ₁₆ H ₁₃ Cl ₂ NO ₄	70.5	<0.001
8	2Cl	6Cl	200-201	C	C ₁₆ H ₁₃ Cl ₂ NO ₄	62.8	<0.01
9	3Cl	4Cl	194-195	C	C ₁₆ H ₁₃ Cl ₂ NO ₄	61.5	<0.01
10	3Cl	5Cl	185-186	C	C ₁₆ H ₁₃ Cl ₂ NO ₄	67.9	<0.001
11	2CH ₃	H	149-150	B	C ₁₇ H ₁₇ NO ₄	55.1	<0.001
12	3CH ₃	H	125-126	B	C ₁₇ H ₁₇ NO ₄	51.2	<0.001
13	4CH ₃	H	170-171	B	C ₁₇ H ₁₇ NO ₄	37.1	<0.05
14	2CH ₃	3CH ₃	167-168	C	C ₁₈ H ₁₉ NO ₄	46.1	<0.01
15	4OCH ₃	H	163-164	C	C ₁₇ H ₁₇ NO ₅	44.8	<0.001
16	4OC ₂ H ₅	H	165-166	C	C ₁₈ H ₁₉ NO ₅	47.4	<0.001
17	2CF ₃	H	160-161	B	C ₁₇ H ₁₄ F ₂ NO ₄	42.3	<0.001
18	2CH ₃	5Cl	181-182	B	C ₁₇ H ₁₆ ClNO ₄	46.1	<0.05
19	2CH ₃	4Cl	178-179	B	C ₁₇ H ₁₆ ClNO ₄	41	<0.001
20	2CH ₃	3Cl	188-189	B	C ₁₇ H ₁₆ ClNO ₄	41	<0.01
4HHA						48.7	<0.001

^aA, MeOH; B, *i*-PrOH; C, AcOH. ^bIncrease of reaction time % 3 hr after treatment. ^cDoses were of 30 mg/kg for each group of 10 mice. ^dThe hot plate test counts were analyzed statistically by means of the Student *t* test. *P* was compared to controls.

0.05 mole of substituted anilines. The reaction mixture was refluxed for 2 hr and then diluted with cold H₂O, and the crystalline reaction product was filtered off. It was washed with 5% NaHCO₃ and recrystallized.

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Substituted Thiazolidones as Anticonvulsants†

C. Dwivedi,‡ T. K. Gupta, and Surendra S. Parmar*

Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow University, Lucknow-3, India.
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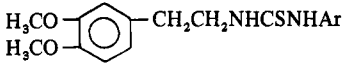
In continuation of our interest^{1,2} in thiazolidones, some new 2-arylimino-3-(3,4-dimethoxyphenethyl)thiazolid-4-ones have been synthesized and tested for their anticonvulsant activity against pentylenetetrazol-induced seizures in albino mice.

Anticonvulsant activity was detd² by injecting the thiazolidone ip in a 5% aqueous suspension of gum acacia in groups of 10 mice of either sex. Pentylenetetrazol (80 mg/kg) was injected 4 hr after the administration of thiazolidones and the mice were then observed for 60 min for the occurrence of seizures. Animals devoid of even a threshold convulsion were considered protected. Anticonvulsant activity shown by substituted thiazolidones at 100 mg/kg is given

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‡ Junior Research Fellow of I.C.M.R., New Delhi.

Table I. Substituted Thiocarbamides

				
No.	Ar	Mp, °C	Yield, %	Molecular formula ^b
1	C ₆ H ₅	125	85	C ₁₇ H ₂₀ N ₂ O ₂ S
2	<i>o</i> -CH ₃ C ₆ H ₄	112	65	C ₁₈ H ₂₂ N ₂ O ₂ S
3	<i>m</i> -CH ₃ C ₆ H ₄	122	78	C ₁₈ H ₂₂ N ₂ O ₂ S
4	<i>p</i> -CH ₃ C ₆ H ₄	92	85	C ₁₈ H ₂₂ N ₂ O ₂ S
5	3,4-(CH ₃) ₂ C ₆ H ₃	125	82	C ₁₉ H ₂₄ N ₂ O ₂ S
6	<i>o</i> -OCH ₃ C ₆ H ₄	108	62	C ₁₈ H ₂₂ N ₂ O ₃ S
7	<i>p</i> -OCH ₃ C ₆ H ₄	120	72	C ₁₈ H ₂₂ N ₂ O ₃ S
8	<i>p</i> -ClC ₆ H ₄	114	80	C ₁₇ H ₁₉ ClN ₂ O ₂ S
9	<i>p</i> -BrC ₆ H ₄	135	80	C ₁₇ H ₁₉ BrN ₂ O ₂ S
10	α-C ₁₀ H ₇	166	68	C ₂₁ H ₂₂ N ₂ O ₂ S

^aMelting points were taken in open capillary tubes. ^bAll compds were analyzed for C, H, and N and analyses were found within 0.4% of theory.

in Table II. Compd 2 having an *o*-tolyl group at position 2 afforded the maximum protection of 70%, while administration in doses above or below 100 mg/kg caused lesser anticonvulsant activity. The low toxicity of this compound was reflected by its approximate LD₅₀ (>2000 mg/kg).

Experimental Section

1-Aryl-3-(3,4-dimethoxyphenethyl)thiocarbamide. 3,4-Dimethoxyphenethylamine (0.01 mole) was mixed with a suitable aryl isothiocyanate (0.01 mole) in 15 ml of dry PhH and was refluxed on a steam bath for 2 hr. The reaction mixt was concd under reduced pressure. The solid mass which sepd on cooling was filtered, washed (Et₂O, dil HCl), dried, and recrystd from EtOH. All thiocarbamides were characterized by their sharp melting points and elemental analyses (Table I).

2-Arylimino-3-(3,4-dimethoxyphenethyl)thiazolid-4-ones. A mixt of 1-aryl-3-(3,4-dimethoxyphenethyl)thiocarbamide (0.01 mole), ClCH₂COOH (0.01 mole), and anhyd NaOAc (0.015 mole) in 15 ml of glacial AcOH was refluxed for 5-6 hr. The reaction mixt was poured into H₂O and refrigerated overnight. The sepd crude product was filtered, washed several times (H₂O), and recrystd from EtOH (Table II).