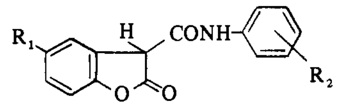
Table I. Physical Properties and Methods of Preparation of 2,3-Dihydro-2-oxobenzofuran-3-carboxanilides



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_6H_6	$C_{16}H_{13}NO_3$	3.57
3	H	3-CH_3	158-159	B[b]	13	C_6H_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_6H_6-hexane	$C_{15}H_{10}FNO_3$	3.22
6	H	4-F	175-177	B	25	C_6H_6-hexane	$C_{15}H_{10}FNO_3$	
7	H	2-Cl	140-142	B	14	C_6H_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*-PrOH-H_2O	$C_{15}H_{10}ClNO_3$	3.42
10	H	4-Br	199-200	B	29	C_6H_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_6H_6	$C_{16}H_{13}NO_4$	4.04
13	Cl	H	186-188	C[b]	46	C_6H_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_6H_6-hexane	$C_{15}H_9Cl_2NO_3$	
17	Cl	4-Cl	222-223	C	25	*i*-PrOH	$C_{15}H_9Cl_2NO_3$	
18	Cl	2-OCH_3	131-132	C	57	C_6H_6-hexane	$C_{16}H_{12}ClNO_4$	
19	Cl	4-OCH_3	208-209	C	69	MeCN	$C_{16}H_{12}ClNO_4$	

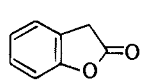
[a]All analyses are within ±0.3% of calcd values. [b]See Experimental Section.

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

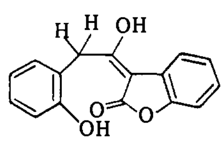
Method B. The appropriate isocyanate was added to equimolar amts of Et_3N and lactone in DMF. After stirring for 30-90 min, the reaction mixt was partitioned between Et_2O or EtOAc and aqueous base. The aqueous layer was sepd and acidified with 6 *N* HCl. The resulting ppt was filtered, dried, and recrystd.

Method C. Identical with method B except that the lactone was added to the Et_3N-isocyanate mixt in DMF.

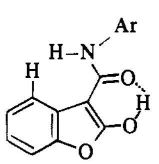
Reaction of I with Diethyl Carbonate. A soln of 5.36 g (0.04 mole) of I in dry THF was added to a cold suspension of 1.6 g (0.04 mole) of a 60% mineral oil dispersion of NaH in THF. Gas was liberated; to the resulting thick suspension there was added, dropwise, 4.72 g (0.04 mole) of diethyl carbonate. After stirring the reaction mixt for 1 hr, during which time room temp was attained, it was dild with 200 ml of H_2O. The aqueous soln was shaken once with Et_2O, 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, CH_2C=O), 10.16 (broad, 2 H, enol and phenol). *Anal.* ($C_{16}H_{12}O_4$) C, H.



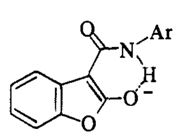
I



II



III



IV

Acknowledgment. The author thanks Dr. E. H. Wiseman of these laboratories for carrying out the biological evaluation of these compounds and Messrs. H. A. Watson and H. E. Wiedermann for expert technical assistance.

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

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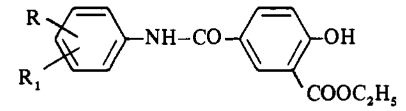
The fact that 4-hydroxyisophthalic acid shows various biological activities, notably analgetic,[1] prompted us to perform the synthesis and some pharmacological evaluation of the title compounds. The standard methods of synthesis are given in the Experimental Section. All the derivatives were tested for analgetic action by the hot plate test[2] using mice weighing 18-22 g. Their activities are listed in Table I. All the derivatives showed low toxicity in mice ($LD_{50} > 650$ mg/kg).

Experimental Section†

General Procedure for the Preparation of the Compounds Described in Table I. The 3-monoethyl ester of 4-hydroxyisophthalic acid[3] (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] $P \leqslant$
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	$C_{16}H_{13}Cl_2NO_4$	64.1	<0.001
6	2Cl	4Cl	164-165	C	$C_{16}H_{13}Cl_2NO_4$	74.3	<0.001
7	2Cl	5Cl	203-204	C	$C_{16}H_{13}Cl_2NO_4$	70.5	<0.001
8	2Cl	6Cl	200-201	C	$C_{16}H_{13}Cl_2NO_4$	62.8	<0.01
9	3Cl	4Cl	194-195	C	$C_{16}H_{13}Cl_2NO_4$	61.5	<0.01
10	3Cl	5Cl	185-186	C	$C_{16}H_{13}Cl_2NO_4$	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	$C_{17}H_{14}F_3NO_4$	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

[a]A, MeOH; B, *i*-PrOH; C, AcOH. [b]Increase of reaction time % 3 hr after treatment. [c]Doses were of 30 mg/kg for each group of 10 mice. [d]The 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 H_2O, and the crystalline reaction product was filtered off. It was washed with 5% $NaHCO_3$ and recrystallized.

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Substituted Thiazolidones as Anticonvulsants†

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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 detd[2] 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 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 LD_{50} (>2000 mg/kg).

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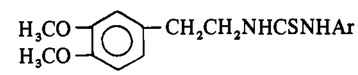
‡Junior Research Fellow of I.C.M.R., New Delhi.

Table I. Substituted Thiocarbamides



No.	Ar	Mp,[a] °C	Yield, %	Molecular formula[b]
1	C_6H_5	125	85	$C_{17}H_{20}N_2O_2S$
2	*o*-CH$_3$C$_6$H$_4$	112	65	$C_{18}H_{22}N_2O_2S$
3	*m*-CH$_3$C$_6$H$_4$	122	78	$C_{18}H_{22}N_2O_2S$
4	*p*-CH$_3$C$_6$H$_4$	92	85	$C_{18}H_{22}N_2O_2S$
5	3,4-(CH$_3$)$_2$C$_6$H$_3$	125	82	$C_{19}H_{24}N_2O_2S$
6	*o*-OCH$_3$C$_6$H$_4$	108	62	$C_{18}H_{22}N_2O_3S$
7	*p*-OCH$_3$C$_6$H$_4$	120	72	$C_{18}H_{22}N_2O_3S$
8	*p*-ClC$_6$H$_4$	114	80	$C_{17}H_{19}ClN_2O_2S$
9	*p*-BrC$_6$H$_4$	135	80	$C_{17}H_{19}BrN_2O_2S$
10	α-C$_{10}$H$_7$	166	68	$C_{21}H_{22}N_2O_2S$

[a]Melting points were taken in open capillary tubes. [b]All compds were analyzed for C, H, and N and analyses were found within 0.4% of theory.

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 (Et_2O, 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), $ClCH_2COOH$ (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 H_2O and refrigerated overnight. The sepd crude product was filtered, washed several times (H_2O), and recrystd from EtOH (Table II).