acid chloride **19** (10.7 g, 0.05 mole) was treated in C_6H_6 with excess of Et_2NH (0.1 mole) and refluxed for 1 hr. The soln was dild with an equal vol of anhyd Et_2O and filtered. The filtrate was washed with 5% HCl, H_2O, and satd salt soln and dried (Na_2SO_4). The solvent was stripped and distd 9.8 g (70.8%), bp 109–114° (0.05 mm).

3-(*N,N*-Diethylaminomethyl)spiro[5.5]undecane (39). The amide **37** (6.9 g, 0.0273 mole) was reduced to the amine in the usual manner in Et_2O with LAH. After the usual work-up the product distd at 72–78° (0.05 mm), 5 g (76.8%), and was converted into its HCl salt, mp 181–182°.

Diethylaminoethyl ester of 3-carboxyspiro[5.5]undecane (57) was prepd by refluxing in C_6H_6 equimolar amts of the acid chloride **19** and diethylaminoethanol. After the usual work-up, the product when recrystd from EtOH–Et_2O had mp 170–171°.

3-Carboethoxyspiro[5.5]undecane (20). A mixt of acid chloride **19** (30 g, 0.139 mole) in 150 ml of C_6H_6 was treated with 50 ml of abs EtOH and refluxed for 0.5 hr. The solvent was removed and the product distd, bp 80–85° (0.15 mm), 26.9 g (86.2%).

3-Hydroxymethylspiro[5.5]undecane (21). The reduction of the ester **20** (25.9 g, 0.115 mole) in Et_2O by LAH gave the product, 20 g (95.8%), bp 87–89° (0.1 mm).

Ethyl 2-Cyano-2-(spiro[5.5]undec-3-yl)acetate (28). A soln of 64.7 g (0.247 mole) of ethyl 2-cyano-2-(spiro[5.5]undecylidene-3-yl)acetate[5] dissolved in 300 ml of abs EtOH was hydrogenated at room temp using 3 g of 10% Pd/C. H_2 uptake was 1.8 kg/cm² (theory 1.7 kg/cm²). After filtering and removal of solvent the residue was distd, bp 147–149° (0.7 mm), to yield 56.8 g (87.3%).

Spiro[5.5]undec-3-ylacetic Acid (22). The cyano ester **28** (56.0 g, 0.21 mole) was refluxed with 300 ml of concd HCl for 24 hr and dild with 300 ml of H_2O. The white gummy material was exted with Et_2O and the Et_2O was evapd. This material was dissilved in a soln of 60 g of KOH in 400 ml of abs EtOH and refluxed for 20 hr. The EtOH was evapd and the K salt was dissolved in H_2O, decolorized by charcoal, and acidified with HCl. The slightly brown ppt of this malonic acid derivative was filtered and dried (mp 143°), 48 g. It was heated at 200° until evoln of CO_2 ceased. The residue was distd, bp 140–142° (0.1 mole), 28 g (55%).

Ethyl (spiro[5.5]undecylidene-3-yl)acetate (25) was prepd from 27 g (0.162 mole) of spiro[5.5]undecan-3-one and triethyl phosphonoacetate as outlined by Wadsworth and Emmons.[6] The product was distd, bp 94–96° (0.03 mm), 27.4 g (71.7%).

Ethyl (Spiro[5.5]undec-3-yl)acetate (26). The unsat ester **25** (47.25 g, 0.2 mole) was hydrogenated in the same manner as **28**. The uptake of H_2 was 1.1 kg/cm² and the product distd, bp 92–93° (0.04 mm), to yield 45.5 g (95.4%). Hydrolysis readily gave **22**.

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Antiinflammatory 2,3-Dihydro-2-oxobenzofuran-3-carboxanilides

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Received September 7, 1971

The discovery,[1] made in these laboratories, that certain β-oxoanilides, *e.g.*, dioxoisoquinoline-4-carboxanilides, which display unusually strong acidic properties also manifest potent antiinflammatory activity has been confirmed in more recent publications.[2-4] The purpose of this communication is to extend these findings by describing the synthesis and some chemical and biological properties of a series of novel carboxanilides derived from 2(3*H*)-benzofuranone (I).

Treatment of I with aryl isocyanates under basic conditions led to the desired 2,3-dihydro-2-oxobenzofuran-3-carboxanilides (Table I). Best yields of the carboxanilides were obtained using an inverse addition procedure in which incipient carbanion derived from I was generated in the presence of excess isocyanate. This procedure presumably minimized a competing reaction in which I undergoes base-catalyzed self-condensation to form II.[5] Only the latter material was isolated when I was allowed to react with diethyl carbonate, a relatively poor electrophile.

The 2,3-dihydro-2-oxobenzofuran-3-carboxanilides display acidic properties (pK_a' 3–4) comparable to those seen in an earlier series.[1,6] Inspection of Ealing-Corey-Pauling-Koltun space-filling molecular models indicates that formation of the resonance-stabilized enol tautomer (III) appears to be precluded because of the severe steric interaction which would be generated between the protons attached to the amide nitrogen and position four of the benzofuranone nucleus. This assumption is confirmed by examination of the nmr and ir spectra. The nmr spectra exhibit signals at *ca.* δ 4.7 representing the proton at position 3 while the ir spectra show strong carbonyl absorptions at *ca.* 5.5 and 6.0 μ. They are, therefore, consistent with the presence of the keto tautomer rather than of III. Rehybridization of the lone sp^3 C at position 3 may be accommodated, however, by ionization in which stability of the resulting anion (IV) is very likely favored by the formation of a H bond between the enolate anion and the proton on the amide N. Thus, both steric hindrance to enolization and enhanced enolate anion stability probably contribute to the singularly acidic characteristics of these carboxanilides.

Antiinflammatory activity was measured by the carrageenin-induced rat foot edema assay.[7] All compounds in Table I demonstrated activity at least equivalent to that evinced by aspirin. In addition, compds **2**, **5**, and **13** exhibited activity at 10 mg/kg equivalent to that shown by aspirin at a dose of 100 mg/kg.

Experimental Section

Melting points are uncorrected. Isocyanates used were commercial materials as was 2-hydroxyphenylacetic acid. Nmr spectra were recorded on a Varian A-60 spectrometer (Me_4Si). pK_a' detns were performed at 25° in 1:2 (v/v) H_2O–dioxane using a Metrohm automatic potentiograph (Model E 436). Compds for which no pK_a' data are reported were insufficiently soluble. Where analyses are indicated only by symbols of the elements, results obtd were within ±0.4% of calcd values.

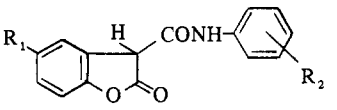
2(3*H*)-Benzofuranone (I). A soln of 38.0 g (0.25 mole) of 2-hydroxyphenylacetic acid in 500 ml of xylene contg a catalytic amt of *p*-TsOH was refluxed for 1.5 hr under a Dean–Stark trap. After evapn of the xylene the residual oil was distd to yield 30.0 g (90%) of I, bp 132–134° (18 mm), mp 43–45° (lit.[8] mp 49°).

5-Chloro-2-hydroxyphenylacetic acid was prepd from 5-chloro-2-methoxybenzaldehyde[9] according to the method of Levine, *et al.*,[10] for the prepn of 2-hydroxyphenylacetic acid, mp 128–129.5°. *Anal.* ($C_8H_7ClO_3$) C, H.

5-Chloro-2(3*H*)-benzofuranone. Prepared as described above for 2(3*H*)-benzofuranone except that PhH was used in place of xylene, mp 127–129°. *Anal.* ($C_8H_5ClO_2$) C, H.

Method A. A soln of lactone in DMF was added to a cold suspension of an equimolar amount of a mineral oil dispersion of NaH in DMF. Gas was liberated; immediately after addn was complete the appropriate isocyanate was added dropwise. Tlc at this point showed no starting material remaining and the reaction mixt was

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	$C_{16}H_{12}ClNO_4$	

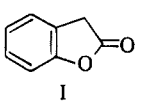
[a] All analyses are within ±0.3% of calcd values. [b] See Experimental Section.

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

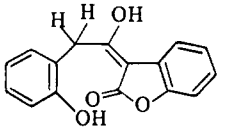
Method B. The appropriate isocyanate was added to equimolar amts of Et_3N and lactone in DMF. After stirring for 30-90 min, the reaction mixt was partitioned between Et_2O or EtOAc and aqueous base. The aqueous layer was sepd and acidified with 6 *N* HCl. The resulting ppt was filtered, dried, and recrystd.

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



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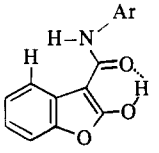

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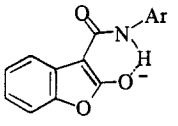

IV

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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Received October 28, 1971

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.