Table III. Physical Properties

No.	Method,[a] % yield	Mp, °C (recrystn solvent)[b]	Emperical formula	Analyses[c,d]
1	A, 67	84.5-84.6 (A)	$C_{12}H_{13}NO_2$	
2	A, 74	77-79 (A)	$C_{13}H_{15}NO_2$	
3	A, 52	74-75 (B)	$C_{13}H_{15}NO_2$	
4	A, 45	72-73 (A)	$C_{14}H_{17}NO_2$	
5	B, 83	86-88 (C)	$C_{13}H_{14}FNO_2$	C, H, N
6	B, 77	63-65 (C)	$C_{13}H_{14}ClNO_2$	C, H, Cl, N
7	B, 75	35 (A)	$C_{14}H_{17}NO_2$	C, H, N
8	B, 61	66-68 (C)	$C_{14}H_{17}NO_3$	C, H, N, O
9	B, 91	119-120 (C)	$C_{13}H_{13}Cl_2NO_2$	C, H, Cl, N
10	B, 66	69-71 (C)	$C_{15}H_{19}NO_2$	C, H, N, O
11	B, 90	114-116 (D)	$C_{11}H_{13}NO_2S$	C, H, N, S
12	C, 54	87-89 (D)	$C_{13}H_{16}FNO_3$	C, H, N
13	C, 53	85-87 (D)	$C_{13}H_{16}ClNO_3$	C, H, N, O
14	C, 66	101-102 (D)	$C_{14}H_{19}NO_3$	C, H, N
15	C, 62	100-102 (D)	$C_{14}H_{19}NO_4$	C, H, N, O
16	C, 53	159-162 (D)	$C_{13}H_{13}Cl_2NO_3$	C, H, Cl, N
17	C, 52	65-67 (A)	$C_{15}H_{21}NO_3$	C, H, N, O
18	C, 41	95-97 (D)	$C_{11}H_{15}NO_3S$	C, H, N, S

[a] See Experimental Section. [b] A, Et_2O; B, EtAc; C, CH_2Cl_2-pentane; D, CH_2Cl_2-Et_2O. [c] Unless otherwise stated the analyses are within ±0.4% of the theoretical values. [d] Analyses for 1-4 are given in ref 5.

give the 8a-aryl-3,4,6,7,8,8a-hexahydro-2*H*-pyrrolo[2,1-*b*][1,3]-oxazin-6-ones (**5-11**) given in Table III.

Method C. General Procedure. A stirred mixture of 3-aroylpropionic acid (0.10 mol), triethylamine (0.10 mol), and 250 ml of chloroform was cooled to 0° and then treated dropwise with a solution of ethyl chloroformate (0.10 mol) in 100 ml of $CHCl_3$ at such a rate that the internal temperature did not excede 10°. After an additional 2.5 h of stirring the mixture was treated dropwise with 3-aminopropanol (0.10 mol). The cooling was removed and the reaction was stirred for ca. 20 h at room temperature. The $CHCl_3$ layer was decanted, washed with H_2O, 1 N HCl, and saturated NaCl, respectively, and then dried with anhydrous Na_2SO_4. The solution was filtered and the solvent removed in vacuo to give the *N*-(3-hydroxypropyl)-3-aroylpropionamides (**12-18**) in Table III.

Acknowledgment. The authors are grateful to Mrs. Nancy Engstrom and Mr. Urs Stoeckli for instrumental determinations and to Mr. William Bonkoski for the microanalyses.

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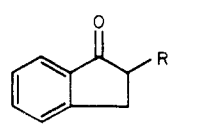
Potentiation of the Estrogenic Activity of Stilbestrol by Spiro(cyclohexane-1,2'-indan)-1',4-dione

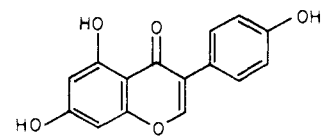
David J. Bailey,* Neil S. Doggett, Lai Yin Ng, and Tariq Qazi

Welsh School of Pharmacy, Uwist, Cardiff, Wales. *Received August 18, 1975*

During the investigation of a series of spiro compounds having approximately similar molecular dimensions to naturally occurring estrogens, the novel compound spiro(cyclohexane-1,2'-indan)-1',4-dione was prepared. The pretreatment of mice with this estrogenically inactive compound was found to potentiate the estrogenic activity of stilbestrol.

The present investigation is concerned with the synthesis and biological activity of one of a series of spiro compounds having approximately similar molecular dimensions to some naturally occurring estrogens. During a routine pharmacological screening program it was found that pretreatment with the estrogenically inactive compound spiro(cyclohexane-1,2'-indan)-1',4-dione (**1b**), which is structurally related to the estrogenic isoflavone genistein (**2**),[1] potentiated the estrogenic activity of stilbestrol.





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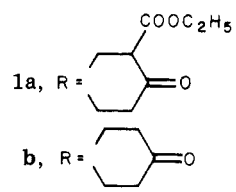

Chemistry. 2,2-Bis(β-ethoxycarbonylethyl)indanone was prepared by a two-step Michael condensation between indanone and ethyl acrylate. Ring closure was accomplished by a Dieckmann reaction followed by hydrolysis and decarboxylation to give spiro(cyclohexane-1,2'-indan)-1',4-dione (**1b**).

Pharmacological Activity. Quantitative estimations of estrogenic activity were made using the immature mouse uterine response assay procedure previously described by Rubin et al.[2]

The results presented in Table I show that, whereas **1b** alone is devoid of any significant estrogenic activity at doses of up to 100 μg per mouse, it does produce a marked potentiation in the estrogenic activity of stilbestrol when the two drugs are given in combination. Furthermore, an indication of the potency of **1b** was revealed when it was found that this effect is consistently detectable, although not statistically significant, at a dose level as low as 0.1 μg per mouse. However, in order to attain significant ($p < 0.05$ at 100 μg) potentiation it was essential that **1b** was given at least 24 h before stilbestrol, since experiments in which this pretreatment period was absent revealed no

Table I. Estrogenic Potentiation in Mice by Spiro(cyclohexane-1,2'-indan)-1',4-dione

Group	Treatment	Wt of mouse (g), mean ± SE	Wt of uterus (mg), mean ± SE	Uterine ratio
1	Arachis oil, 0.1 ml	12.1 ± 0.7	28.0 ± 2.0	232.2 ± 10.4
2	Stilbestrol, 0.1 μg	16.8 ± 0.5	148.1 ± 7.9	881.5 ± 70.2
3	**1b**, 0.1 μg	14.1 ± 0.4	35.5 ± 2.8	251.6 ± 19.5[a]
4	**1b**, 100 μg	13.3 ± 0.7	28.3 ± 2.1	212.7 ± 10.4[a]
5	**1b**, 0.1 μg, + stilbestrol, 0.1 μg	15.2 ± 0.7	145.0 ± 12.8	957.1 ± 72.6[b]
6	**1b**, 100 μg, + stilbestrol, 0.1 μg	14.1 ± 0.5	192.3 ± 12.6	1366.9 ± 79.5[c]

[a] Not significant ($p > 0.05$) when compared with arachis oil control. [b] Not significant ($p > 0.05$) when compared with stilbestrol (0.1 μg) control. [c] $p < 0.05$ when compared with stilbestrol (0.1 μg) control.

such effects.

In the light of these preliminary findings, the investigation of related compounds in this chemical series appears justified, since the use of an intrinsically inactive compound which will, nevertheless, potentiate estrogenic activity may be of value in reducing the undesirable side effects associated with the clinical use of a wide range of estrogenic drugs.

Experimental Section

Melting points were determined using a capillary apparatus and were uncorrected. Ir spectra were recorded on a Perkin-Elmer 357 spectrophotometer and uv spectra with a Pye Unicam SP800 spectrophotometer. NMR spectra were determined on a Varian HA-100 spectrometer using tetramethylsilane as an internal standard. Where analyses are indicated only by symbols of the elements, the results obtained for those elements are within ±0.4% of theoretical values. Elemental analyses were performed by Mr. G. Crouch, School of Pharmacy, University of London.

2-(β-Ethoxycarbonylethyl)indanone. Ethyl acrylate (12 g, 0.12 mol) was added to a well-stirred mixture of α-indanone (14.4 g, 0.10 mol), triton B (2 ml), and hydroquinone (2 mg) in dioxane (50 ml) at such a rate that the temperature was maintained at about 50°. After addition was complete the reaction mixture was stirred at room temperature for a further 18 h before pouring into H_2O (100 ml) and extracting with $CHCl_3$ (three times). The combined $CHCl_3$ extract was dried (Na_2SO_4) and evaporated in vacuo and the residue distilled to afford the title compound (13.1 g, 51.7%): bp 170–180° (0.4 mm) [lit.[3] bp 208–209° (13 mm)].

2,2-Bis(β-ethoxycarbonylethyl)indanone. The title compound was prepared according to the procedure described for 2-(β-ethoxycarbonylethyl)indanone. The crude product was distilled, bp 190–195° (1.0 mm), to yield a colorless oil (7.0 g, 48.9%): ir (film) 1750 (five-membered cyclic C=O), 1730 cm^{-1} (ester C=O). Anal. ($C_{19}H_{24}O_5$) C, H.

Spiro(3-ethoxycarbonylcyclohexane-1,2'-indan)-1',4-dione (1a). The above indanone (23.2 g, 0.1 mol) was gradually added to a well-stirred suspension of metallic sodium (2.0 g) in dry toluene (150 ml) under an atmosphere of N_2 at 100 °C. After the vigorous reaction had subsided the mixture was refluxed for 4 h, cooled, and acidified with 10% AcOH. The mixture was extracted with $CHCl_3$ (three times); the combined $CHCl_3$ extracts were washed with H_2O and aqueous Na_2CO_3 and dried (Na_2SO_4). The $CHCl_3$ was evaporated and the residue distilled in vacuo to afford **1a** (12.1 g, 42.2%): bp 182–190° (0.7 mm); ir (film) 1740 (β-keto ester C=O), 1720 (β-ester keto C=O), 1710 cm^{-1} (aromatic C=O); uv (EtOH) 247 nm (ε 50). Anal. ($C_{17}H_{18}O_4$) C, H.

Spiro(cyclohexane-1,2'-indan)-1',4-dione (1b). A mixture of the dione **1a** (6.4 g, 0.03 mol) in 50% aqueous EtOH (100 ml) and HCl (33%, 40 ml) was boiled under reflux for 6 h and then poured into H_2O (250 ml). The mixture was extracted with Et_2O (three times). The combined Et_2O extracts were washed with H_2O and aqueous $NaHCO_3$ and dried (Na_2SO_4). Evaporation gave a residue which distilled in vacuo to afford an oil, bp 156–158 °C (0.7 mm), which slowly crystallized from Et_2O (4.0 g, 83.6%): mp 75 °C; ir (KBr) 1715 (six-membered cyclic C=O), 1705 cm^{-1} (aromatic C=O); NMR ($CDCl_3$) δ 7.45 (4 H, aromatic ring), 3.25 (2 H, $-ArCH_2C-$), and 2.5 (8 H, $-CH_2CH_2C=O$); uv (EtOH) 269 nm (ε 583). Anal. ($C_{14}H_{14}O_2$) C, H.

Pharmacological Results. Female albino mice of an ICI strain, 23–25 days old, were randomly distributed into groups of ten. Groups 1–4 received no treatment on the first day, followed by arachis oil (0.1 ml), stilbestrol (0.1 μg), and **1b** (0.1 or 100 μg), respectively, once daily for three consecutive days. Groups 5 and 6 received **1b** (0.1 or 100 μg) on the first day, followed by **1b** (0.1 or 100 μg) together with stilbestrol (0.1 μg), on each of the three following days. All compounds were administered by subcutaneous injection in 0.1 ml of arachis oil. The group receiving vehicle alone served as controls. Free access to food and water was allowed throughout the experiment. The mice were sacrificed by cervical dislocation 24 h after the last injection and the body and uterine weights were determined. Uterine ratios were then calculated as uterine wt (mg)/body wt (g) × 100.

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Book Reviews

Chemistry of Winemaking. Edited by A. Dinsmoor Webb. American Chemical Society, Washington, D.C. 1974. viii + 311 pp. 16 × 23.5 cm. $16.95.

A. Dinsmoor Webb and 12 contributors have presented 13 papers discussing all aspects of wine production including specific aspects of commercial and home wine making. These original contributions published in this "Advances in Chemistry Series" were written in mid-1973 by various specialists belonging mainly to the Department of Viticulture and Enology of the University of California, in Davis, as well as to well-known Institutes from France, Germany, and the trade.

The chemistry of wine making as a biological-technological sequence, discussed by F. Drawert, describes the influence of each step in the process of wine making on the chemical composition of the chemical components in the wine. The composition of grapes, as well as other fruits such as apples, pears, cherries, blackberries, and strawberries, is discussed by J. F. Gallander. This complete review (277 references are cited in literature) deals with water, sugars, and organic acids which are essential for the quality of wine. Vitamins, enzymes, pectins, aromatic volatiles, and nitrogenous and phenolic substances such as anthocyanins are also discussed. The chemistry of red color is discussed by P. Ribereau-Gayon, a well-known wine analyst. After describing the different anthocyanins and tannins which give red wine its color and organoleptic character, a practical method of classi-