Structure and Antitumor Activity Relationship of 2-Arylidene-4-cyclopentene-1,3-diones and 2-Arylideneindan-1,3-diones

Seiichi Inayama,* Katsuhiro Mamoto, Tetsuichi Shibata, and Tadaaki Hirose

Pharmaceutical Institute, Medical School, Keio University, Shinjuku-ku, Tokyo, Japan. *Received July 15, 1975*

A series of 2-arylidene-4-cyclopentene-1,3-diones and 2-arylideneindan-1,3-diones, as well as mono- and bis(arylidene substituted)cycloalkanones, was synthesized and examined for antitumor activity against ascites sarcoma-180. All the 2-arylidene-4-cyclopentene-1,3-diones and one arylideneindan-1,3-dione (where the arylidene group was either a hydroxybenzylidene or substituted hydroxybenzylidene) exhibited a high degree of activity. Among both types of 1,3-diones the 3-methoxy-4-hydroxybenzylidene derivatives were found to possess the greatest potency, while all the mono- and bis(arylidene)cycloalkanones were found to be inactive.

Unique sesquiterpene alkaloids such as pulchellidine and neopulchellidine and also various types of sesquiterpenolides containing pseudoguaianolides (such as pulchellin and neopulchellin), guaianolides (such as gaillardin and neogaillardin), and eudesmanolides (such as pulchellin B, C, E, and F) have been isolated from *Gaillardia pulchella*.[1] A common feature of these compounds is the α-methylene-γ-butyrolactone moiety or its equivalent. This functionality also occurs in antitumor germacranolides, e.g., elephantopin, etc., isolated from certain species of *Compositae*.[2] Furthermore, the presence of an α-methylene-γ-lactone has been found to be intrinsically essential for significant cytotoxicity among several sesquiterpenoids, but no monofunctional α-methylene-δ-lactones contributed directly to the cytotoxic activity as in the α-methylene-γ-lactone.[3] On the other hand, the highly unsaturated γ-methylene-$\Delta^{\alpha,\beta}$-butyrolactones are exemplified by the antimicrobial antibiotics, protoanemonin[4] and patulin,[5] from plant and fungi source, respectively. It can be reasonable to consider the α-methylenecyclopentanone structure as a homocyclic alternative of the α-methylene-γ-lactone. Both α-methylenecyclopentanone and α-methylene-γ-lactone are arrayed by the equivalent electrophilic function of the α-methylenecarbonyl grouping. It is deemed plausible that those may play a significant role as an alkylating agent for biological nucleophiles such as nucleic acid. This analogy led us to believe a concept that certain α-methylenecyclopentanone derivatives would be expected to show antitumor activity. The antitumoral antibiotic, sarkomycin A, is indeed an appropriate example of the analogue, which has been formulated as (−)-β-hydroxycarbonyl-α-methylenecyclopentanone.[6] However, this kind of low molecular α-methylenecyclopentanone derivative cannot avoid, more or less, a decrease of the lipophilicity and stability in biological systems.

Our attention was then directed toward the study of the electronic structure of the modified arylidenecyclopentanones[7] based on the α-methylene-γ-lactone and α-methylenecyclopentanone, which might possess a promising tumor inhibitory activity. It is obvious that the electrophilicity of cyclopentene-1,3-dione should be more profound than those of cyclopentane-1,3-dione and cyclopentanone and that α-arylidene substitutents would be more favorable than the α-methylene group for impartation of lipophilicity to the cyclopentenedione moiety. Thus, 2-arylidenecyclopentene-1,3-dione derivatives were assumed to be most convincing for a fruitful achievement. A number of arylidene derivatives of cyclopentene, indan-1,3-diones, and cycloalkanones described in the present communication were prepared by condensation of substituted benzaldehydes with cycloalkanones and cycloalkenediones catalyzed by bases or acids. These compounds were tested for the antitumor activity against ascites sarcoma-180 (Tables I–III). Three features of the parent compound have been modified: the cycloalkane ring, the methylene side chain, and the aromatic nucleus. The structure–activity relationship of these potential antitumoral agents was discussed in detail.

Results and Discussion

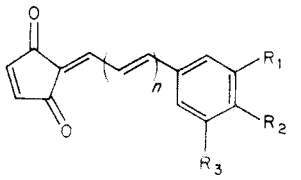
As shown in Table I all substituted benzylidene-4-cyclopentene-1,3-diones exhibited considerable potency against S-180 on administration at 10 mg/kg/day according to Hoshi, Kanzawa, and Kuretani's biological testing method.[8] The (4'-hydroxy-3'-methoxybenzylidene)-4-cyclopentene-1,3-dione (**3**) was the most active, at 3 mg/kg/day, of these compounds. Though the parent compound of this series, 4-cyclopentene-1,3-dione (**1**), was highly toxic, the arylidene derivatives exhibited appreciable antitumor activity with less toxicity. As shown in Table II, (4'-hydroxy-3'-methoxybenzylidene)indan-1,3-dione (**14**) was the most active among several arylideneindandione series as well as the cyclopentenedione series but was approximately $^1/_{30}$th the relative potency of the corresponding compound **3**. It should be worthy to note in this series of compounds that a methoxy or a hydroxy group at both para and meta positions of the benzilidene moiety may be required for antitumor activity. For example, the inactive compounds, such as **13**, **16**, and **20–23**, shown in Table II, have no methoxy or hydroxy group. Elimination of the endo and/or exo double bond in conjugation with the carbonyl of the arylidenecyclopentenedione series resulted in loss of the activity. It is of interest to add that bis(arylidene)cyclopentanone and cyclohexanone analogues, shown in Table III, all lacked activity as did the several monoarylidene derivatives mentioned above.

The mechanism of action at the molecular level of compounds listed in Tables I and II is unknown at the moment. However, the biological activity of certain related α,β-unsaturated γ-lactones has been reported to be linked to a reaction with the genetic material of the cell, apparently interfering with DNA and RNA syntheses,[9] but not to be correlated directly to the rate of cysteine addition.[3]

Experimental Section

The procedures given in this section were representative for each of the analogous compounds presented in Tables I–III. The melting points were taken on a Buchi (capillary tube) apparatus and are uncorrected. The ir spectra were recorded on a Hitachi EPI-G3 instrument and the uv spectra were determined on a Shimazu UV-200 spectrophotometer in the solvents, as noted. The ^{1}H NMR spectra were measured on a JEOL C-60H NMR spectrometer in the solvents as noted and the values are in δ (ppm) measured downfield from Me_4Si as a standard. The elemental composition data for C and H were within ±0.4% of the calculated values and the empirical formulas for each compound are listed in Tables I–III.

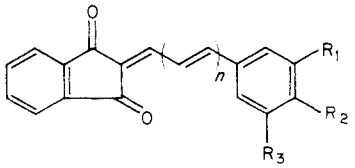
Table I. 2-Arylidene-4-cyclopentene-1,3-dione Analogues[a]



No.	n	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield, %	Formula[b]	Dose,[c] mg/kg/day	Evaln[d]
1		Cyclopentene-1,3-dione			30-32				3	Toxic
2	0	H	OH	H	208-209	MeOH	31	$C_{12}H_8O_3$	10	+++
3	0	H	OH	OCH_3	197-199	MeOH	34[e]	$C_{13}H_{10}O_4$	3	+++
4	0	OCH_3	OH	OCH_3	179.5-181.5	MeOH	40	$C_{14}H_{12}O_5$	10	+++
5	0	H	OCH_3	H	164-166	$CHCl_3$-EtOH	33	$C_{13}H_{10}O_3$	10	+++
6	0	H	OCH_3	OH	207-208	MeOH	34	$C_{13}H_{10}O_4$	10	+++
7	0	H	OCH_3	OCH_3	153-154	$CHCl_3$-MeOH	38	$C_{14}H_{12}O_4$	10	+++
8	0	OCH_3	OCH_3	OCH_3	145-147	MeOH	40	$C_{15}H_{14}O_5$	10	+++
9	0	H	OCH_2Ph[f]	OCH_3	163-165	EtOH	30[g]	$C_{20}H_{16}O_4$	10	++
10	0	OCH_3	OCH_2Ph	OCH_3	169.5-171	EtOH	65	$C_{21}H_{18}O_5$	10	++
11	1	H	H	H	192-196	MeOH	19	$C_{14}H_{10}O_2$	10	+++

[a] All compounds were obtained by condensation of substituted benzaldehydes with appropriate cycloalkanones according to the general procedure as exemplified by the representative experiment described in the Experimental Section. [b] Compounds were analyzed for C and H and analytical values were with in ±0.4% of the calculated values. [c] See Experimental Section. [d] TPCV %: 100-66 (−), 65-41 (+), 40-11 (++), 10-0 (+++). [e] 24% of yield was given when treated with concentrated HCl or refluxed in AcOH solution containing a small amount of concentrated H_2SO_4. [f] Ph is noted for C_6H_5 (phenyl). [g] Successful preparation was made only by the method using H_2SO_4-AcOH (70°, 2 h).

Table II. 2-Arylideneindan-1,3-dione Analogues[a]



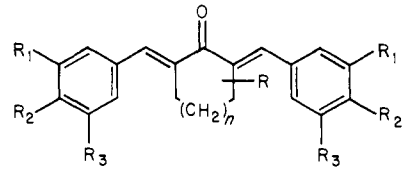
No.	n	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield, %	Formula[b]	Dose,[c] mg/kg/day	Evaln[d]
12		Indan-1,3-dione			129-131				100	++
13	0	H	OH	H	237-239	AcOH	64	$C_{16}H_{10}O_3$	100	−
14	0	H	OH	OCH_3	213-215[e]	EtOH	67[f]	$C_{17}H_{12}O_4$	100	+++
15	0	OCH_3	OH	OCH_3	231-232	$CHCl_3$-EtOH	61	$C_{18}H_{14}O_5$[g]	100	++
16	0	H	OCH_3	H	155-157	$CHCl_3$-EtOH	74	$C_{17}H_{12}O_3$	100	−
17	0	H	OCH_3	OCH_3	204-206	$CHCl_3$-EtOH	74	$C_{18}H_{14}O_4$	100	+
18	0	H	OCH_3	OH	230-236	$CHCl_3$	75	$C_{17}H_{12}O_4$	100	+
19	0	OCH_3	OCH_3	OCH_3	185.5-187	$CHCl_3$-MeOH	67	$C_{19}H_{16}O_5$	100	+
20	0	H	OCH_2Ph[h]	OCH_3	178-179	EtOH	70[i]	$C_{24}H_{18}O_4$	100	−
21	0	OCH_3	OCH_2Ph	OCH_3	165-168	$CHCl_3$-EtOH	75	$C_{25}H_{20}O_5$	100	−
22	1	H	H	H	153-155[j]	MeOH-$CHCl_3$	60[k]	$C_{18}H_{12}O_2$	100	−
23	1	H	OH	OCH_3	224-226	$C_4H_8O_2$	55	$C_{19}H_{14}O_4$	100	−

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] See Experimental Section. [d] See footnote *d*, Table I. [e] Mp 212° is reported by St V. Kostanecki, *Ber. Dtsch. Chem. Ges.*, **30**, 1183 (1897). [f] 61% of yield was obtained when refluxed in aqueous NaOH for 13 h. [g] C: calcd, 69.67; found, 70.15. [h] See footnote *f*, Table I. [i] 78% of yield was given when treated with AcOH containing a small amount of piperidine. [j] Mp 150-151° is reported by Kostanecki, see footnote *e*. [k] 72% of yield was given when refluxed with TsOH-$CHCl_3$ for 1.5 h.

A. **Syntheses. 2-(4'-Hydroxy-3'-methoxybenzylidene)-4-cyclopentene-1,3-dione (3).** In a typical procedure for the preparation of the cyclopentenedione derivatives listed in Table I, a mixture of 4-cyclopentene-1,3-dione[10] (0.96 g, 0.01 mol), 4-hydroxy-3-methoxybenzaldehyde (1.52 g, 0.01 mol), and TsOH (0.25 g) was refluxed in anhydrous CH_2Cl_2 or $CHCl_3$ (40 ml) for 2–4 days. To the cooled reaction mixture was added water (20 ml), and the organic layer was separated, dried ($MgSO_4$), and then evaporated to give a crystalline mass. Recrystallization from MeOH afforded 0.77 g (34% of the theoretical amount) of yellow needles: mp 197–199°; uv (99% C_2H_5OH) λ max 221 nm (ε 16600), 245 (9100) (infl), and 384 (22100); ir (KBr) 3390 (OH), 1723 (C=O), and 1685, 1673, 1618 cm^{-1} (C=C); NMR (CF_3COOH) δ 4.38 (s, 3, OCH_3), 8.05–8.17 (m, 3, >C=CH–, –CH=CH–), 7.68–9.16 (m, 3, arom H). Anal. ($C_{13}H_{10}O_4$) C, H. All other new 2-arylidene-4-cyclopentene-1,3-dione analogues described in Table I were synthesized in a similar manner.

2-(4'-Hydroxy-3',5'-dimethoxybenzylidene)indan-1,3-dione (15). In a general procedure, the following method was used for preparation of the indandione derivatives listed in Table II. Indan-1,3-dione (1.46 g, 0.01 mol) and 4-hydroxy-3,5-dimethoxybenzaldehyde (1.82 g, 0.01 mol) were dissolved in EtOH (60 ml) containing two drops of piperidine. The solution was refluxed for 1–2 h. The crystalline product which separated on cooling from the reaction mixture was filtered and recrystallized from EtOH–$CHCl_3$ to yield 1.55 g (61%) of yellow needles: mp 231–232°; uv (99% C_2H_5OH) λ max 249 nm (ε 23000), 260 (17600) (infl), 439 (25500), and 540 (12100); ir (KBr) 3482 (OH), 1720 (C=O), 1672, 1620, 1570, 1510 cm^{-1} (C=C); NMR ($CDCl_3$) δ 4.05 (s, 6, OCH_3), 7.77–8.08 (m, 8, arom H, OH, and >C=CH–). Anal.

Table III. Bis(arylidene)cycloalkanone Analogues[a]



No.	n	R	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield, %	Formula[b]	Dose,[c] mg/kg/day	Evaln[d]
24	0	H	H	OH	OCH_3	214-216	EtOH	70	$C_{21}H_{30}O_5$	100	-
25	0	H	H	OCH_3Ph[e]	OCH_3	164-165	$CHCl_3$-MeOH	52	$C_{35}H_{32}O_5$	100	-
26	0	H	OCH_3	OH	OCH_3	238-242	EtOAc	71	$C_{23}H_{34}O_7$	100	-
27	0	H	OCH_3	OCH_3Ph	OCH_3	181-183	$CHCl_3$-MeOH	52	$C_{37}H_{36}O_7$	100	-
28	1	H	H	OH	OCH_3	180-182[f,g]	AcOH-H_2O	95	$C_{22}H_{32}O_5$	100	-
29	1	H	H	OCH_3Ph	OCH_3	172.5-174	AcOH-H_2O	79	$C_{36}H_{34}O_5$	100	-
30	1	H	OCH_3	OH	OCH_3	178-179	AcOH-EtOH	60	$C_{24}H_{36}O_7 \cdot C_2H_6O$	100	-
31	1	H	OCH_3	OCH_3Ph	OCH_3	136-138	EtOH	63	$C_{38}H_{38}O_7 \cdot 5H_2O$	100	-
32	1	m-CH_3	H	OH	OCH_3	171-173.5[h]	MeOH-Et_2O	40	$C_{23}H_{34}O_5$	100	-
33	1	m-CH_3	H	OCH_3Ph	OCH_3	132.5-134	Me_2CO	67	$C_{37}H_{36}O_5$	100	-
34	1	m-CH_3	OCH_3	OH	OCH_3	200-202	MeOH	21[i]	$C_{25}H_{38}O_7 \cdot H_2O$	100	-
35	1	m-CH_3	OCH_3	OCH_3Ph	OCH_3	123.5-125	Me_2CO	53	$C_{39}H_{40}O_7$	100	-
36	1	m-CH_3	OCH_3	OCH_3	OCH_3	206.5-209.5	$CHCl_3$-MeOH	70	$C_{26}H_{30}O_7$	100	-
37	1	p-CH_3	H	OH	OCH_3	168.5-169.5[j]	MeOH	74	$C_{23}H_{34}O_5$	100	-
38	1	p-CH_3	H	OCH_3Ph	OCH_3	144-145	Me_2CO	82	$C_{37}H_{36}O_5$	100	-
39	1	p-CH_3	OCH_3	OH	OCH_3	190-192	MeOH	63	$C_{25}H_{38}O_7 \cdot 0.5H_2O$[k]	100	-
40	1	p-CH_3	OCH_3	OCH_3Ph	OCH_3	117-119	MeOH	74	$C_{39}H_{40}O_7 \cdot 0.5H_2O$	100	-

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] See Experimental Section. [d] See footnote *d*, Table I. [e] See footnote *f*, Table I. [f] Mp 179° (cor) is reported by D. Vorländer and O. Koch, *Ber. Dtsch. Chem. Ges.*, **62**, 534 (1929). [g] Mp 179-180° is reported by M. B. Samdahl, *J. Pharm. Chim.*, **7**, 162 (1928). [h] Mp 171-172° is reported by Samdahl, see footnote *g*. [i] Together with 3-methyl-6-(3',5'-dimethoxy-4'-hydroxybenzylidene)cyclohexanone, mp 108-109° (MeOH), in 32% yield. [j] Mp 169° is reported by Samdahl, see footnote *g*. [k] C: calcd, 66.80; found, 66.34.

($C_{18}H_{14}O_5$) C, H. The preparation of the other new arylideneindan-1,3-dione analogues was performed by the same method.

2,6-Bis(4'-hydroxy-3',5'-dimethoxybenzylidene)cyclohexanone (30). A general procedure for preparation of the bis(arylidene)cycloalkanone derivatives listed in Table III was performed according to the procedure of an Austrian patent.[11] Cyclohexanone (1.47 g, 0.015 mol), 4-hydroxy-3,5-dimethoxybenzaldehyde (1.82 g, 0.01 mol), and three drops of concentrated HCl were mixed and stirred at 70° for 1 h. The product, upon solidification, was added to cold aqueous AcOH (1:1) with stirring. The crystalline material which separated was filtered, washed with hot water, and dried (1.56 g, 73%). Recrystallization from dilute AcOH (4:1) and EtOH afforded 1.28 g (60%) of yellow needles: mp 178–179°; uv (99% C_2H_5OH) λ max 258 nm (ε 16300) and 396 (31600); ir (KBr) 3475, 3400 (OH), 1656 (C=O), 1604, 1589, 1513 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.65–3.54 (m, 6, $>CH_2$), 3.98 (s, 12, OCH_3), 5.93 (s, 2, OH), 6.83 (m, 8, arom H), 7.78 (m, 2, >C=CH–). Anal. ($C_{24}H_{26}O_7$) C, H. Several other bis(arylidene)cyclohexanone and -cyclopentanone analogues were prepared by the same method.

Monoarylidenecycloalkanone derivatives were prepared in poor yield (3–28%) by condensation of the morpholino enamines of 2-, 3-, and 4-methylcyclohexanone with the substituted benzaldehydes, as above. A typical procedure is the preparation of 6-(3',5'-dimethoxy-4'-hydroxybenzylidene)-3-methylcyclohexanone.

The morpholino derivative of 3-methylcyclohexanone, prepared in the usual manner [1.08 g, 0.006 mol, bp 134–137° (20 mm)], was refluxed with 3,5-dimethoxy-4-hydroxybenzaldehyde (0.91 g, 0.005 mol) in absolute benzene (5 ml) for 20 h. Dilute HCl (1:1) (3 ml) was added dropwise into the cooled reaction mixture with stirring. The organic layer was separated, washed with water, and then evaporated in vacuo. The crystalline residue was digested, washed with warm petroleum ether, and then recrystallized twice from MeOH to yield 6-(3',5'-dimethoxy-4'-hydroxybenzylidene)-3-methylcyclohexanone (0.13 g, 6%): mp 108–109°; mass spectrum (70 eV) M^+ 276.3345; uv (99% C_2H_5OH) λ max 250 nm (ε 8700) and 345 (13700); ir (KBr) 3440 (OH), 1668 (C=O), 1603, 1593, 1567, 1517 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.03 (d, 3, J = 6 Hz, $>CHCH_3$), 1.57–2.95 (m, 7, $>CH_2$, ≡CH), 3.89 (s, 6, OCH_3), 5.90 (br s, 1, OH), 6.57 (s, 2, arom H), 7.38 (br s, 1, >C=CH–). Anal. ($C_{16}H_{20}O_4$) C, H.

The 2-(3'-methoxy-4'-hydroxybenzylidene)cyclopentane-1,3-dione was prepared as follows. To a NaH solution in Me_2SO (5 ml), cyclopentane-1,3-dione (0.098 g, 0.001 mol) and benzylvanillin (0.242 g, 0.001 mol) were added and the solution was heated at 70° for 2 h. The reaction mixture was poured onto ice water, neutralized with dilute HCl, and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$), and chromatographed on neutral Al_2O_3. Elution with Et_2O–$CHCl_3$ (1:1) gave a crystalline product of 2-(3'-methoxy-4'-hydroxybenzylidene)cyclopentane-1,3-dione (0.21 g, 65%). Recrystallization from EtOH and then chromatography afforded colorless needles: mp 118–121°. Anal. ($C_{20}H_{18}O_4 \cdot 1.75H_2O$) C, H. Unsuccessful results were obtained with $C_5H_{11}N$–EtOH, H_2SO_4–AcOH, and NaOEt–EtOH employed as catalysts for the condensation.

B. Biological Tests.[12] A volume of 0.05 ml (3×10^7 cells) of 7-day-old ascites sarcoma-180 was inoculated intraperitoneally in female ddN mice weighing 20 ± 2 g. Injection was performed once daily for 5 days, following 24 h of postinoculation. The

antitumor activities of all compounds listed in Tables I–III were evaluated with the total packed cell volume ratio (TPCV %) on the 7th day after the tumor inoculation, as reported previously.[9]

Acknowledgment. One of the authors (S.I.) acknowledges in part the Scientific Research Fund from the Ministry of Education of Japan for the present work. They are gratefully indebted to Drs. K. Kuretani and A. Hoshi of NCC of Japan for making available the antitumor screening results and valuable discussion. They also thank Miss K. Nakaji of Joint Laboratory of this school for the uv and ir spectral measurements.

References and Notes

(1) S. Inayama, T. Kawamata, and M. Yanagita, *Phytochemistry*, 12, 1741 (1973), and references cited herein.
(2) S. M. Kupchan, Y. Aynehchi, J. M. Cassady, A. T. McPhail, G. A. Sim, H. K. Schnoes, and A. L. Burlingame, *J. Am. Chem. Soc.*, 88, 3674 (1966).
(3) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, 14, 1147 (1971).
(4) H. Baer, M. Holden, and B. C. Seegal, *J. Biol. Chem.*, **162**, 65 (1946).
(5) R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 1428 (1950).
(6) I. R. Hooper, L. C. Cheney, M. J. Cron, O. B. Fordig, D. A. Johnson, D. L. Johnson, F. M. Palermiti, H. Schmitz, and W. B. Wheatley, *Antibiot. Chemother.*, **5**, 585 (1955).
(7) A correlation between electronic distribution and biological activity of various arylidenecyclopentene-1,3-diones will be reported elsewhere.
(8) A. Hoshi, F. Kanzawa, and K. Kuretani, *Chem. Pharm. Bull.*, 17, 848 (1969).
(9) P. Brookes and P. D. Lawley, *Br. Med. Bull.*, **20**, 91 (1964); F. Dickens, *ibid.*, **20**, 96 (1964), and references cited therein.
(10) "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 324.
(11) W. Rumpel, Austrian Patent 180258 (1954).
(12) The antitumor screening against ascites sarcoma-180 was carried out by Dr. A. Hoshi of the Pharmacology Division of the Research Institute of National Cancer Centre and the test results were kindly made available through the courtesy of Dr. K. Kuretani of the same Institute as above.

Synthesis and Central Nervous System Depressant Activity of Some Bicyclic Amides

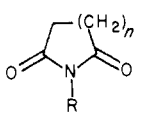
Paul Aeberli, John H. Gogerty, William J. Houlihan,* and Louis C. Iorio

Research and Development Department, Sandoz Pharmaceuticals, Hanover, New Jersey 07936. *Received September 2, 1975*

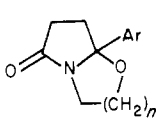
A series of aryl bicyclic analogs of succinimide and glutarimide was prepared and evaluated for CNS depressant activity. The 8a-aryl-3,4,6,7,8,8a-hexahydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6-ones possessed the best overall spectrum of activity relative to the standard agents glutethimide and phenobarbital.

A large number of five- and six-membered heterocyclic compounds containing a dicarboximide unit (O=CNC=O) have been reported to possess CNS activity.[1-3] The simplest members of this class, the succinimides (Ia) and glutarimides (Ib), have depressant activity and are used as anticonvulsants,[2] sedatives,[1,3] and muscle relaxants.[1]

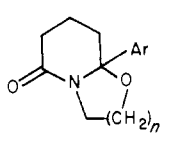
In the present work we have prepared a series of aryl bicyclic analogs II[4] and III[4] where one of the carbonyl groups in I has been incorporated as part of a second heterocyclic ring and evaluated these compounds for CNS depressant activity.



Ia, $n = 1$
Ib, $n = 2$



IIa, $n = 1$
IIb, $n = 2$



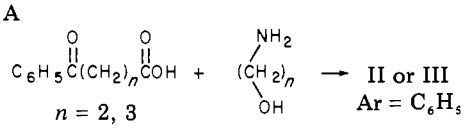
IIIa, $n = 1$
IIIb, $n = 2$

Chemistry. The phenyl analogs of II and III described in this work were prepared by the previously reported[5] condensation of the corresponding oxo acid with an alkanolamine (method A).

Substituted phenyl and 2-thienyl derivatives of IIb were obtained by thermal cyclizations of the *N*-hydroxyalkylamides IV in refluxing xylene in the presence of an acid catalyst (method B). The uv spectra of several hydroxyamides indicated they prefer to exist in the open-chain ketone IV form rather that the cyclic tautomer V.

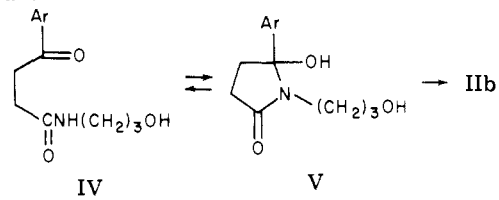
Pharmacology. The results obtained when the bicyclic amides II and III were evalulated in a series of behavioral

method A



$n = 2, 3$ $n = 1, 2$ Ar = C_6H_5

method B



IV V

and drug-interaction tests in mice designed to uncover CNS depressant activity are given in Table I. Anticonvulsant activity was studied in mice, using as criteria the antagonism to *N*-sulfamoylhexahydroazepine[6] (N-SA) and maximal electroshock[7] (MES). General CNS-depressant activity was defined by the ability of a substance to reinduce "anesthesia" following loss of righting reflex obtained with hexobarbital.[8]

Evaluation of the phenyl analogs 1–4 of the four ring systems given in formulas II and III revealed that the 3,4,6,7,8,8a-hexahydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6-one (IIb) derivative **2** possessed the best overall spectrum relative to the standards glutethimide (VI) and phenobarbital (VII).

In an attempt to improve the activity of **2** the phenyl ring was substituted with F (**5**), Cl (**6**), CH_3 (**7**), OCH_3 (**8**), Cl_2 (**9**), and $(CH_3)_2$ (**10**) groups or replaced by a 2-thienyl