Benzylideneindenes with Oxygen Attached to the Indene Ring[1,2]

CARL TABB BAHNER, DAVID H. BROTHERTON, AND HAROLD KINDER

Department of Chemistry, Carson-Newman College, Jefferson City, Tennessee 37760

Received March 6, 1969

It has been suggested that one possible change produced by metabolism of 1-(4-dimethylamino)benzylidene (I) might be hydroxylation at the 5 or 6 position on the indene. The hydroxy compound might itself be a major active metabolite, or it might be converted to the methoxy compound. A different suggestion has been that an unsubstituted 5 position may be essential for activity. We have prepared the three methoxyindenes shown in Table I, and all three have been found to be active against Walker 256 tumors, at least two being toxic at lower dose levels than I. One or more of them could be metabolites of I and could account for part of the antitumor activity and toxicity of I. Other methoxy compounds deserve attention.

Preparation of the methoxyindenes involved preparation of indanones as intermediates. Several ketones were condensed with aldehydes to produce other compounds listed in Table I. The three which have been tested against the Walker 256 tumors were inactive, but one was somewhat toxic.

Experimental Section

The 1-indanes with methoxy or methyl groups substituted in the aromatic ring were prepared by a cyclodehydration method similar to the procedure of Bone and Cort.[3] The synthesis of 5-methoxy-1-indanone and 7-methoxy-1-indanone was from β-(*m*-methoxyphenyl)propionic acid. The 6-methoxy-1-indanone was obtained from β-(*p*-methoxyphenyl)propionic acid. The 5,6- or 6,7-dimethoxy-1-indanone was prepared from β-(3,4-dimethoxyphenyl)propionic acid.

The 5- and 6-methoxy-1-indanones were reduced with LAH in THF to yield 6-methoxyindene and 5-methoxyindene. The 5,6- or 6,7-dimethoxy-1-indanone was similarly reduced to produce 5,6-, 4,5-, or 6,7-dimethoxyindene. The substituted indenes were purified by vacuum distillation. When the dimethoxyindene was condensed with 4-dimethylaminobenzaldehyde, a single product was isolated which indicated that only one dimethoxyindene was produced. Designations of positions of the methoxy groups in the final products is tentative, but is believed to be as indicated in Table I.

In a typical preparation of the substituted 2-benzylidene-1-indanones and 1-benzylideneindenes equal molar quantities of the aldehyde and 1-indanone or indene were dissolved in absolute EtOH and heated to boiling, then ethanolic KOH was added slowly until a marked color change from yellow to green-black occurred. This mixture was boiled 30 min, cooled, filtered, and recrystallized.

The substituted 1,3-bisbenzylidene-2-indanone was prepared by dissolving 4.0 g (0.03 mole) of 2-indanone and 8.0 g (0.05 mole) of 4-dimethylaminobenzaldehyde in absolute EtOH and adding 10 ml of concentrated HCl. This acid mixture was re-

TABLE I

DERIVATIVES OF METHOXYINDENES AND INDANONES

Compd	Yield, %	Mp, °C[a]	Formula[b]	KB cell test,[c] ED_{50}, μg/ml	Effect[d] Tumor wt T/C	Effect[d] mg/kg	Lethality No. killed	Lethality mg/kg
1-(4-Dimethylaminobenzylidene)-5,6-dimethoxyindene	37[e]	154–155	$C_{20}H_{21}NO_2$	27	0.50	40	0/3	80
					0.17	80	2/2	125
5- or 6-methoxyindene	33	105–106	$C_{19}H_{19}NO$	30	0.10	160	0/3	320
					0	320	2/2	625
5- or 6-methoxyindene	18[f]	177–178	$C_{19}H_{19}NO$	30	0.06	200	0/3	800
					0.11	800		
2-(4-Dimethylaminobenzylidene)-1-indanone[g]	66	167–169	$C_{18}H_{17}NO$	100	0.9	400	0/3	1600
5-methoxy-1-indanone[h]	73	167–168	$C_{19}H_{19}NO_2$					
7-methoxy-1-indanone[h]	7	186–187	$C_{19}H_{19}NO_2$					
2-{4-[N,N-Bis(2-chloroethyl)amino]-benzylidene}-1-indanone	75	202–204	$C_{20}H_{19}NOCl_2$	100	0.9	1600	0/3	1600
2-(2,5-Dimethoxy-4-dimethylamino-benzylidene)-1-indanone[h]	89	167–168	$C_{20}H_{21}NO_3$					
1,3-Bis(4-dimethylaminobenzylidene)-2-indanone	38[i]	199–200	$C_{27}H_{26}N_2O$		1.11	1600	0/3	1600
1,3-Bis(4-dimethylaminobenzylidene)-2-indanone[h]	38[i]	258–259	$C_{27}H_{26}N_2O$	100				
2-(4-Dimethylaminobenzylidene)-1,3-indanedione	90[i]	206–207	$C_{18}H_{15}NO_2$	100	1.11	160	0/3	160
							2/3	320

[a] Corrected for thermometer stem exposure; determined with Thiele tube. [b] All compounds were analyzed for C and H by Galbraith Laboratories; analytical results were within ±0.3% of the theoretical values. [c] Results of the standard *in vitro* KB tumor cell inhibition tests carried out under sponsorship of the Cancer Chemotherapy National Service Center at Southern Research Institute and University of Miami Cell Culture Laboratory. [d] We are grateful to Professor Sir Alexander Haddow, Mr. J. E. Everett, and Mr. C. V. Mitchley of the Chester Beatty Research Institute for data on toxicity and activity against the Walker 256 tumor in rats weighing 200–250 g. Each compound was administered as a single intraperitoneal injection in arachis oil on the day following tumor implantation or on the first day of the toxicity observation. Tumor-bearing animals were sacrificed approximately 8 days later. [e] All compounds are yellow unless indicated otherwise. [f] Orange. [g] Y. Poirier and N. Lozac'h, *Bull. Soc. Chim. France*, 1062 (1966). [h] Test results not available for these compounds in the Walker system. [i] Red.

(1) This investigation was supported by Public Health Service Research Grants CA-03717-07 and -08 from the National Cancer Institute.

(2) Presented in part at the Southeastern Regional Meeting of the American Chemical Society in Charleston, W. Va., Nov 1965.

(3) A. H. Bone and L. A. Cort, *J. Chem. Soc.*, 1986 (1962).

fluxed 2 hr and allowed to cool. The crystals which formed were dissolved in MeOH, neutralized with NaOH, and purified by fractional recrystallization (C_6H_6–Me_2CO) yielding two isomers.

The substituted 2-benzylidene-1,3-indanedione was prepared by dissolving equal molar quantities of the aldehyde and indanedione in absolute EtOH, heating until crystal formation occurred, cooling, filtering, and recrystallizing from 95% EtOH and Me_2CO.

6-Dimethylaminochrysene and Other Analogs of 4-(4-Dimethylamino)stilbene[1]

CARL TABB BAHNER, DAVID H. BROTHERTON, HAROLD KINDER, WILLIAM RICH, STUART L. WATSON, JR., AND JOHN ZIRKLE

Department of Chemistry, Carson-Newman College, Jefferson City, Tennessee 37760

Received March 6, 1969

6-Aminochrysene (I) has been reported to be active against mammary carcinoma.[2] Noting that a *cis*-4-aminostilbene structure can be seen in one of the Kekule formulas for this compound, we prepared 6-dimethylaminochrysene (Table I) by methylating I with MeI for

TABLE I

ANALOGS OF 4-(4-DIMETHYLAMINO)STILBENE

No.	Compd	Mp, °C[a]	Formula[b]
1	6-Dimethylaminochrysene	101–102[c]	$C_{20}H_{17}N$
2	2-(4-Aminophenyl)indole	215[d]	$C_{14}H_{12}N_2$
3	3-(4-Dimethylaminobenzylidene)oxindole	241–242[e]	$C_{17}H_{16}N_2O$
4	1-(4-Dimethylaminocinnamylidene)indene	205–208[f]	$C_{20}H_{19}N$
5	5-(4-Dimethylaminobenzylidene)hydantoin	286–288[g]	$C_{12}H_{13}N_3O_2$
6	2′-Chloro-4-methylaminostilbene[h]	40–41[i]	$C_{15}H_{14}NCl$[j]
7	2,5-Dimethoxystilbene[h]	51[i]	$C_{16}H_{16}O_2$[j]

[a] Determined with Mel-Temp apparatus. Recrystallization solvents are given as footnotes for each compound. [b] All compounds were analyzed for C and H by Galbraith Laboratories except where indicated otherwise. Analytical results obtained were within ±0.3% of the theoretical values. [c] Pentane and absolute EtOH. [d] *i*-PrOH. [e] 95% EtOH and C_6H_6. [f] Absolute ethanol. Chromatographed on Florisil with C_6H_6, then recrystallized. [g] 95% EtOH. [h] Test results not available for these compounds in the Walker system. [i] Purified by chromatographing on Florisil with C_6H_6. [j] Analysis by Weiler and Strauss.

testing against the Walker 256 tumor. It was effective at dose levels of 240–1500 mg/kg without killing any of the animals, whereas the NH_2 compound was more toxic, killing two of the test animals at 625 mg/kg, but was more effective than the $N(CH_3)_2$ compounds at lower dose levels.

2-(4-Aminophenyl)indole, prepared by catalytic reduction of the 4-nitro compound[3] with Pd catalyst in EtOAc, can be considered as a *trans*-4-aminostilbene, but was inactive against the Walker tumor (Table II).

3-(4-Dimethylaminobenzylidene)oxindole, an analog of 1-(4-dimethylaminobenzylidene)-2-indanone, was prepared by the usual KOH-catalyzed condensation method. It was inactive against the Walker tumor.

(1) This investigation was supported by Public Health Service Research Grants CA-03717-05–11 from the National Cancer Institute.

(2) J. Gelzer and P. Loustalot, *European J. Cancer*, **3**, 79 (1967).

(3) C. E. Blades and A. L. Wilds, *J. Org. Chem.*, **21**, 1013 (1956).

TABLE II

No.[a]	KB cell test,[b] ED_{50}, μg/ml	Effect[c] Tumor wt T/C	Effect[c] Tumor wt mg/kg	Lethality No. killed	Lethality mg/kg
1		0.5	240	0/3	1500
		0.2	600		
2		1.0	400[d]	0/6	400[d]
3	100	0.8	1280	0/3	1280
4	100	1.0	1500	0/3	1500
5		0.9	1600	0/3	1600
6	6				

[a] See Table I for names of compounds. [b] Results of the standard *in vitro* KB tumor cell inhibition tests carried out under sponsorship of the Cancer Chemotherapy National Service Center at Southern Research Institute and University of Miami Cell Culture Laboratory. [c] We are grateful to Professor Sir Alexander Haddow, Mr. J. E. Everett, and Mr. C. V. Mitchley of the Chester Beatty Research Institute for data on toxicity and activity against the Walker 256 tumor in rats weighing 200–250 g. Each compound was admintered as a single intraperitoneal injection in arachis oil on the day following tumor implantation or on the first day of the toxicity observation. Tumor-bearing animals were sacrificed approximately 8 days later. [d] We are grateful to CCNSC for screening tests against Walker 256 in random-bred albino rats, using four daily intraperitoneal injections in CMC or peanut oil administered 3 days after implantation and sacrificed 7 days after implantation.

The importance of space relations in determining the activity of 1-(4-dimethylaminobenzylidene)indene is demonstrated by the inactivity of 1-(4-dimethylaminocinnamylidene)indene in which the conjugated series of double bonds has been lengthened to the extent of one more ethylene group. 5-(4-Dimethylaminobenzylidene)hydantoin was inactive and nontoxic.

2′-Chloro-4-methylaminostilbene and 2,5-dimethoxystilbene were prepared by treating the appropriate aldehyde with Grignard reagent prepared from benzyl chloride or 2-chlorobenzyl chloride. The 2′-chloro compound was more toxic in KB cell culture than the methoxy compound.

9-(4-Aminobenzylidene)fluorenes[1]

CARL TABB BAHNER AND DAVID BROTHERTON

Department of Chemistry, Carson-Newman College, Jefferson City, Tennessee 37760

Received March 6, 1969

Haddow, *et al.*,[2] found that 9-(4-dimethylaminobenzylidene)fluorene (I) had some antitumor effect. We have synthesized I and three of its analogs shown in Table I. The Walker 256 tumor inhibition test as now carried out is apparently less sensitive than the test originally used, since the only carcinostatic result obtained was a 38% reduction in the size of tumors treated with 9-(4-methylaminobenzylidene)fluorene. The ED_{50} values in the standard KB tissue culture tests were of the same order of magnitude as for the 1-(4-methylaminobenzylidene)indene.[3]

(1) This investigation was supported by Public Health Service Research Grants CA-03717-07 and -08 from the National Cancer Institute.

(2) A Haddow, R. J. C. Harris, G. A. R. Kon, and E. M. F. Roe, *Phil. Trans. Roy. Soc. Lon.*, **241**, 149 (1948).

(3) C. T. Bahner, H. Kinder, D. Brotherton, J. Spiggle, and L. Gutman, *J. Med. Chem.*, **8**, 390 (1965).