Analogs of 1-(4-Dimethylaminobenzylidene)indene. Modifications of the Amino Group[1]

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Variations of the amino group of 1-(4-dimethylaminobenzylidene)indene (I) provide some of the most attractive avenues for modifying the molecule and possibly for obtaining compounds with special advantages. Our publications have reported activity against Walker 256 tumors by several such compounds.[2,3]

1-(4-*N*-Methylacetamidobenzylidene)indene is one of the probable metabolic products from I and 1-(4-methylaminobenzylidene)indene (II). It is important to know whether it is effective against tumors and whether it is toxic. The compound was prepared from II with Ac_2O and was found to be active against Walker Muscular tumors at about the same MED as I, but to be toxic at a much lower dose level than the MLD for I. The related compounds, 1-(4-isobutyrylaminobenzylidene)idene and 1-(4-*N*-isobutyryl-*N*-methylaminobenzylidene)indene have been prepared with the thought that they would be less likely to be carcinogenic than I.

TABLE I: ANALOGS OF 1-(4-DIMETHYLAMINOBENZYLIDENE)INDENE

No.	Compd	Mp, °C[a]	Recrystn solvent[b]	Formula[c]	Effect[d] Tumor wt, T/C	Effect[d] Total dose, mg/kg	Lethality[d] No. killed	Lethality[d] mg/kg
	1-(4-X-Benzylidene)indene							
1	Isopropyl[e]	63–64[g]	aE, I	$C_{19}H_{18}$	0.83	1600	0/7	1600
2	Bromo	124–125	I	$C_{16}H_{11}Br$	0.91	1600	0/6	1600
3	Iodo	127–128	aE, IE	$C_{16}H_{11}I$	0.95	1600	0/6	1600
4	Hydroxy[h]	139		$C_{16}H_{12}O$[i]	0.76	625[j]	0/3	625[j]
5	Cyano[j,k]	137–138	I, aE	$C_{17}H_{11}N$				
6	Methylthio	137	O, aE	$C_{17}H_{14}S$	1.0	1500[j]	0/3	1500[j]
					0.71	1600	0/6	1600
7	*N*-Methylacetamido	119–120	I	$C_{19}H_{17}NO$	0.19	200	0/7	800
					0.08	800	7/13	1600
8	Isobutyrylamino	198–200	IE, IP	$C_{20}H_{19}NO$	0.20	100[j]	0/3	250[j]
					0	250[j]		
9	*N*-Isobutyryl-*N*-methylamino	88	IE, IP	$C_{21}H_{21}NO$	0	1500[j]	1/3	1500[j]
10	Guanylamino	179	B, IE	$C_{17}H_{15}N_3$	1.0	50[j]	0/3	50[j]
					0.31	200	3/3	100[j]
							2/6	200
11	Guanyl-*N*-methylamino[j]	174[l]	B, IE	$C_{18}H_{17}N_3$				
12	(α-Indene-1-ylidene-*p*-tolyl)urea	199[m]	B, iP	$C_{17}H_{14}N_2O$	0.83	10[j]		
13	1-(4-Dimethylaminobenzylidene)indene methiodide	203	W	$C_{19}H_{20}NI$			3/6	300
14	Schiff base of 1-(4-aminobenzylidene)indene and 4-dimethylaminobenzaldehyde	184–185[l]	B, O	$C_{25}H_{22}N_2$	0.20	600[j]	0/3	1500[j]
15	4-(4-Methylthiostyryl)quinoline	92, 102[n]	aE, I	$C_{18}H_{15}NS$	0.83	50[j]	0/3	8[j]
							2/3	125
16	4-(4-Methylthiostyryl)quinoline methiodide[o,j]	265–267	A	$C_{19}H_{18}INS$				
17	2,3,6,7-Tetrahydro-9-(inden-1-ylidenemethyl)-1*H*,5*H*-benzo[*i,j*]quinolizine	147–148[l,p]	I	$C_{22}H_{21}N$	0.73	1600	0/7	1600
18	1-(α-Inden-1-ylidene-*p*-tolyl)-3,3-dimethyltriazene	129–131	I, M, A	$C_{18}H_{13}N_3$	0.25	50[j]	0/3	125[j]
					0	125[j]		

[a] Determined with Mel-Temp melting point apparatus. [b] Solvents used in sequence listed: A, Me_2CO; aE, abs EtOH; B, C_6H_6; E, 95% EtOH; I, commercial mixed branched hexanes; IE, *i*-Pr_2O; IP, *i*-PrOH; O, commercial mixed branched octanes; W, H_2O; M, MeOH. [c] All compounds were analyzed for C and H; analytical results were within ±0.5% of the theoretical values. [d] We are grateful to CCNSC for screening tests against intramuscular implants of Walker 256 tumors in random bred albino rats, using 4 daily ip injections in CMC or peanut oil administered 3 days after implantation; rats were sacrificed 7 days after implantation. The total of the 4 doses is listed. [e] Bernthsen, *Justus Liebigs Ann. Chem.*, **415**, 283; Beilstein, "Handbuch der Organischen Chemie," 4th ed, 1st Suppl., Springer-Verlag, Berlin, 1930, p 342. [f] Test results not available for these compd in the solid Walker system. [g] All compd are yellow except where indicated otherwise. [h] Ruhemann, *J. Chem. Soc.*, **97**, 461. [i] Not analyzed. [j] We are grateful to Professor Sir Alexander Haddow, Professor A. B. Foster, 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 ip injection in arachis oil or in 10% dimethylacetamide 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. [k] Results of the standard *in vitro* KB tumor cell inhibition test, ED_{50} 100 μg/ml; carried out under sponsorship of the CCNSC at Southern Research Institute and University of Miami Cell Culture Laboratory. [l] Orange. [m] Melting point apparatus preheated to melting point. [n] When heated slowly melted at 92°, solidified, and melted at 102°. [o] ED_{50} 23 μg/ml. [p] Purified further by chromatographing on silica gel and eluting with C_6H_6.

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(1) This investigation was supported by Public Health Service Research Grants CA-03717-07-12 from the National Cancer Institute.

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

(3) C. T. Bahner, D. Brotherton, and M. K. Brotherton, *ibid.*, **11**, 401 (1968).

TABLE II: WALKER ASCITES SURVIVAL TEST

No.	Dose	Survivors	T/C
1	400	6/6	126
6	400	6/6	229
7	50	6/6	115
	100	6/6	351
	200	6/6	295
	400	6/6	113
	800	6/6	145
8	400	6/6	229
10	50	4/6	31
17	400	6/6	124

Both were active against the WM tumor. See Tables I and II.

1-(4-Isopropylbenzylidene)indene was prepared because its shape should be almost identical with I. It showed slight activity in the Walker ascites survival test.[4]

1-(4-Iodobenzylidene)indene, 1-(4-bromobenzylidene)indene, 1-(4-cyanobenzylidene)indene, and 1-(4-hydroxybenzylidene)indene were prepared in order to learn whether a halogen, CN, or OH could take the place of the amino group. Both halogen compounds and the hydroxy compound were inactive against the WM tumor.

1-(4-Methylthiobenzylidene)indene, 1-(4-methylthiostyryl)quinoline, and 1-(4-methylthiostyryl)quinoline methiodide were prepared because the sulfide is like the amino group in ability to react with MeI and presumably in ability to enter into a conjugated resonance system. The indene derivative was active against the Walker tumor in the ascitic form.

(4) CCNSC test in which the rats received an ip injection of 10^6 tumor cells in ascitic fluid and the following day received a single dose of the drug. The effectiveness is evaluated by the life survival span.

The condensation product of julolidene aldehyde with indene was of particular interest, since it seemed improbable that this product would be carcinogenic. Unfortunately, it was also inactive against WM tumors. This inactivity might be due to the size of the groups attached to N, for 1-(4-dibutylaminobenzylidene)indene was inactive. The Schiff base formed by condensation of 1-(4-aminobenzylidene)indene and 4-dimethylaminobenzaldehyde was active against the Walker tumor in spite of its high molecular weight.

The methiodide of I was more soluble in water than I, but was lethal at 80 mg/kg ip.

1-(4-Guanylaminobenzylidene)indene and (α-inden-1-ylidene-*p*-tolyl)urea were found to be more toxic than I, and were not effective against WM tumors at the maximum tolerated dose.

Diazotization of 1-(4-aminobenzylidene)indene has opened the door to preparation of many compounds. One of the first of these was the 3,3-dimethyltriazene prepared by coupling the diazonium salt with Me_2NH. Clarke, *et al.*,[5] and Burchenal and coworkers[6] have reported the activity of 3,3-dimethyl-1-phenyltriazene against Sarcoma 180.

TABLE III

PREPARATION OF 1-(4-DIMETHYLAMINOBENZYLIDENE)INDENES

Base	Mole	Acid	Mole	Yield, %	Mp, °C
Piperidine	0.025	Glacial AcOH	0.035	56	160–163
Piperidine	0.025	Glacial AcOH	0.035	52	157–160[a]
Piperidine	0.025	Glacial AcOH	0.035	61	158–161[b]
Piperidine	0.025	Glacial AcOH	0.035	13	159–161[c]
Piperidine	0.025	Glacial AcOH	0.035	21	156–158[d]
Piperidine	0.035	Glacial AcOH	0.050	54	158–160
Piperidine	0.050	Glacial AcOH	0.050	64	159–161
Piperidine	0.025	Glacial AcOH	0.017	42	157–160
Piperidine	0.025	Glacial AcOH	0.069	58	159–162
Pyrrolidine	0.025	Glacial AcOH	0.035	50	158–160
Hexamethylenimine	0.025	Glacial AcOH	0.035	59	160–161
n-Bu_2NH	0.025	Glacial AcOH	0.035	35	159–161
Morpholine	0.025	Glacial AcOH	0.035	5	151–156
Triethylenediamine	0.025	Glacial AcOH	0.035	0	
Pentylamine	0.025	Glacial AcOH	0.035	0	
Piperidine	0.035	Ac_2O	0.021	35	161–163
	0.025	Ac_2O	0.080	0	*e*
Piperidine	0.025	$EtCO_2H$	0.035	55	159–160
Piperidine	0.025	Succinic acid	0.0175	47	163–164
Piperidine	0.025	H_3BO_3	0.0080	0	
Piperidine	0.025	H_3PO_4	0.102	0	
Piperidine	0.050	*p*-TsOH	0.025	68	159–164
Piperidine	0.025	*p*-TsOH	0.0125	73	157–159
Piperidine	0.025	*p*-TsOH	0.0125	93	158–160[f]
Piperidine	0.025	*p*-TsOH	0.0063	70	156–159
Pyrrolidine	0.025	HCO_2H	0.035	0	

[a] 25% Excess aldehyde; [b] 25% Excess indene. [c] C_6H_6 solvent. [d] Xylene solvent. [e] Refluxed for 15 min with catalyst only, then added companents. [f] 200% Excess indene.

Experimental Section

The styrylquinoline was prepared by heating lepidine·HCl and aldehyde together for 2 hr at about 150–155°, cooling, neutralizing, and recrystallizing from C_6H_{14} and from MeOH. The styrylquinolinium compd was prepared by boiling for 2 hr a soln of equimolar quantities of lepidine methiodide and methylthiobenzaldehyde in MeOH with piperidine as a catalyst, cooling, filtering, and recrystallizing from Me_2CO.

(5) D. A. Clarke, R. K. Barclay, C. C. Stock, and C. S. Rondestvedt, Jr., *Proc. Soc. Exp. Biol. Med.*, **90**, 484 (1955).

(6) J. H. Burchenal, M. K. Dabb, M. Beyer, and C. C. Stock, *ibid.*, **91**, 398 (1956).

The KOH-catalyzed condensations of indene with aldehydes were carried out by adding KOH in EtOH gradually to a boiling soln of equimolar quantities of aldehyde and indene until a very dark color change appeared, then boiling for 30 min, cooling, filtering, and recrystallizing. Julolidene aldehyde, however, was difficult to condense with indene by this method, but condensed well when piperidine acetate in PhMe was the catalyst.[7] We have investigated the condensation method with the results in Table III. Unless otherwise indicated, 0.050 mole of aldehyde and 0.050 mole of indene were refluxed 10 hr in PhMe with catalyst. The soln was chilled and filtered, and then washed with 100 ml 50% MeOH, dried, and weighed. In most cases yields were only a little larger after 10 hr heating than after 5 hr. The Dean–Stark trap continued to collect a little H_2O.

(1) The fact that increasing indene:aldehyde ratio increased the yield slightly suggests that a by-product may be formed from 2 moles of aldehyde per mole of indene. (2) PhMe appeared much better than C_6H_6 or xylene. (3) Increasing the amounts of AcOH and of piperidine to 0.05 mole increased the yield. (4) Decreasing amounts of AcOH and of piperidine reduced the yields. (5) Pyrrolidine was slightly less useful than piperidine; hexamethyleneimine slightly more effective than piperidine. (6) Bu_2NH was less effective, morpholine much less effective, triethylenediamine and pentylamine were ineffective. (7) Propionic acid was a little slower and succinic acid about equal to AcOH, but formic, boric, and H_3PO_4 acid were ineffective. (8) Ac_2O in place of AcOH reduced the yield.

The Schiff base was prepared by heating a mixture of equimolar quantities of 1-(4-aminobenzylidene)indene and 4-dimethylaminobenzaldehyde 30 min in an oil bath at 125°. The methiodide of I was prepared by heating a soln of 5 g of I and 4.85 g of MeI in 50 ml of $PhNO_2$ for 8 days at 50°.

1-(4-Guanylaminobenzylidene)indene was formed by dropwise addition of a 50% aq soln of cyanamide to a boiling soln of 1-(4-aminobenzylidene)indene·HCl in *n*-BuOH, cooling, filtering, removing excess starting material by extraction with C_6H_6, dissolving in MeOH, making basic with NaOH, evaporating to dryness, and recrystallizing from *i*-Pr_2O, then from C_6H_6. 1-(4-Methylguanylbenzylidene)indene was prepared similarly, but the reaction mixture was refluxed for 2 hr. Its water solubility was than 2 mg/ml at room temp.

In the diazotization of 1-(4-aminobenzylidene)indene, a soln of 13.1 g of 1-(4-aminobenzyeidene)indene in 180 ml of AcOH and 12 g of 12 *M* HCl and 100 ml of ice H_2O was diazotized at 0° by adding 4.2 g of $NaNO_2$ in 60 ml of ice and H_2O slurry. This mixture was then added gradually to 800 ml of 25% Me_2NH, keeping the temp about 5°. The ppt was filtered and washed with H_2O.

The urea derivative was prepared by adding 0.040 mole of KCNO to 0.040 mole of 1-(4-aminobenzylidene)indene in 100 ml of glacial AcOH, allowing the mixture to stand for 1 hr, adding gradually to 200 ml of H_2O, and filtering. The ppt was washed with 400 ml of H_2O, dried, and extracted with hot C_6H_6 to remove C_6H_6-soluble starting material. The solid was dissolved in hot *i*-OPrH and H_2O was added to the soln until just cloudy, then the soln was chilled and filtered.

(7) E. D. Parker and A. Furst, *J. Org. Chem.*, **23**, 201 (1958).

5′-Diazogriseofulvin

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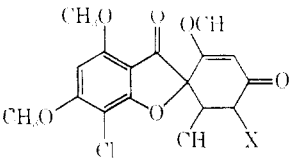
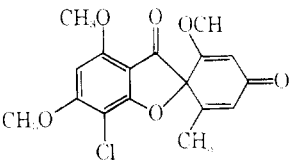
In continuing with our program to prepare analogs of the highly active antifungal drug griseofulvin[1] (**1**) we describe here the preparation of 5′-diazogriseofulvin (**2**) and a few of its transformations. Compound **2** was particularly attractive as a potential intermediate for the preparation of a variety of 5′-griseofulvin derivatives as a result of our finding[1] that 5′-bromogriseofulvin (**3**) failed to undergo the usual displacement reactions of α-halo ketones.

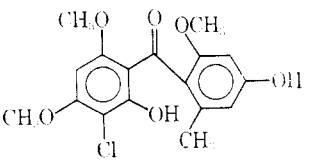
The preparation of **2** was achieved by allowing the readily available 5′-formylgriseofulvin[1] (**3a**) to react with tosylazide[2] in CH_2Cl_2 in the presence of Et_2NH.[3]



1. X = H
2. X = N_2, no 5′-H
3. X = Br
3a. X = CHO
4. X = OCOCH
7. X = SCOCH



5



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An attempt to convert **2** into 5′-acetoxygriseofulvin (**4**) with AcOH gave a rather complex mixture which was partially resolved by partition chromatography into a mixture of **4** and dehydrogriseofulvin **5**,[4] the major products of the reaction. Brief treatment of the mixture of **4** and **5** with Zn and AcOH converted the latter into the base-soluble phenol **6**[4] thus permitting the isolation of 5′-acetoxygriseofulvin (**4**) obtained as a mixture of cis–trans (6′-CH_3 *vs.* 5′-$OCOCH_3$) epimers in a 30:70 ratio (cis:trans).

With thioacetic acid, **2** was converted into 5′-thioacetoxygriseofulvin (**7**), indicated by nmr spectroscopy to be essentially a single isomer (trans 6′-CH_3/5′-SAc). No dehydrogriseofulvin appears to have been formed.

An attempted conversion of **2** into the 5-membered ring C derivative **8** by an Arndt–Eistert reaction using Ag_2O in refluxing MeOH[5] gave instead a mixture consisting of 5′-methoxygriseofulvin (**9**) and dehydrogriseofulvin (**5**). An attempt to effect this rearrangement photochemically[6] gave a complex mixture which could not be resolved.[7]

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(1) For previous papers in this series see H. Newman and T. Fields, *J. Org. Chem.*, in press, and ref cited therein.

(2) W. von E. Doering and C. H. DePuy, *J. Amer. Chem. Soc.*, **75**, 5955 (1953). Tosyl azide is now commercially available from Eastman Organic Chemicals, Rochester, N. Y.

(3) M. Rosenberger, P. Yates, J. B. Hendrikson, and W. Wolf, *Tetrahedron Lett.*, 2585 (1964).

(4) D. Taub, C. H. Kuo, H. L. Slates, and N. C. Wendler, *Tetrahedron*, **19**, 1 (1963).

(5) W. E. Bachmann and W. S. Struve, *Org. React.*, **1**, 38 (1942); W. Kirmse, "Carbene Chemistry," Academic, New York, N. Y., 1964, p 119.

(6) See A. Schonberg, G. O. Schenck, and O. A. Neumuller "Preparative Organic Photochemistry" 2nd ed, Springer-Verlag, New York, N. Y., 1968, Chapter 32, p 295.

(7) For a review of the various reactions α-diazoketones undergo see F. Weygand and H. J. Bestmann, "Newer Methods of Preparative Organic Chemistry," Vol. III, Academic Press, New York, N. Y., 1964, p 451.