analysis showed it to be a mixture of three sterols. The mixture was analyzed using an instrument[4] fitted with a 0.63-cm. (0.25-in.) o.d. × 1.8-m. (6-ft.) glass column packed with Gas Chrom Q, 100–120 mesh, and coated with 5% OV-101. Helium was used (80 ml./min.) as the carrier gas, and the column was maintained at 250°. Cholestane was used as the internal standard. The sterols were identified as campesterol (15.6%), stigmasterol (6.2%), and β-sitosterol (78.2%) by comparison of the relative retention times of the eluted sterols with reference samples of authentic sterols.

[4] Perkin-Elmer model 881.

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Synthesis of Potential Antineoplastic Agents XXII: Compounds Related to 1-Nitro-3-[(*p*-phenylbenzylidene)amino]guanidine

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Abstract □ The nitroguanylhydrazone of 4-biphenylcarboxaldehyde exhibits antineoplastic activity in the Walker 256 and KB test systems. Other nitroguanylhydrazones and other derivatives of 4-biphenylcarboxaldehyde were prepared and found to be devoid of antineoplastic activity.

Keyphrases □ 1-Nitro-3-[(*p*-phenylbenzylidene)amino]guanidine, related compounds—synthesized and screened as potential antineoplastic agents □ Antineoplastic agents, potential—synthesis of compounds related to 1-nitro-3-[(*p*-phenylbenzylidene)amino]-guanidine, screened against Walker 256 and KB test systems □ 4-Biphenylcarboxaldehyde derivatives—synthesized and screened as potential antineoplastic agents □ Nitroguanylhydrazones—synthesized and screened as potential antineoplastic agents

In connection with other work in progress in this laboratory, the nitroguanylhydrazone of 4-biphenylcarboxaldehyde (I) was prepared. In routine screening, this compound was found to possess antineoplastic activity against Walker carcinosarcoma 256 (Table I) and had confirmed activity against KB cell culture. To explore this lead further, a series of nitroguanylhydrazones and some derivatives of 4-biphenylcarboxaldehyde were prepared for screening. Nitroguanylhydrazones were previously used to identify aldehydes and

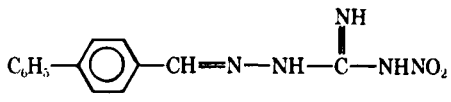

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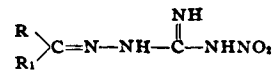
Table I—Summary of Screening of 1-Nitro-3-[(*p*-phenylbenzylidene)amino]guanidine against Walker Carcinosarcoma 256 (Subcutaneous) in Fischer 344 Rats[a]

Vehicle	Day of First Injection	Number of Injections	Dose, mg./kg.	Animal Weight —Percent— Difference T−C[b]	T/C[c]
Hydroxypropylcellulose[d]	1	9	400	−6	150
	1	9	200	−2	138
	1	9	100	−2	116
	3	4	400	−1	166
	3	4	200[e]	1	177
	3	4	100	−2	116
Saline with polysorbate 80	1	9	400	−7	144
	1	9	200	−2	133
	1	9	100	−5	144
	1	9	50	1	150
	3	4	400	−8	144
	3	4	200	−4	127
	3	4	100	1	111

[a] Supplied by Drug Research and Development, Chemotherapy, National Cancer Institute. Intraperitoneal administration was made daily, with evaluation on Day 30. In all cases, there was 6/6 survivors. [b] Average weight change of test group minus average weight change of control animals in grams. [c] Ratio of survival time of treated to control animals expressed as percent. [d] Klucel. [e] Two cures.

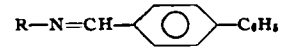
Table II—Nitroguanylhydrazones



Aldehyde or Ketone Used (RR_1CO)	Melting Point	Yield, %	Formula	Analysis, % N Calc.	Analysis, % N Found
4-Biphenylcarboxaldehyde	225–227°	90	$C_{14}H_{12}N_6O_2$	24.72	24.40
Acetylferrocene	205–207°	80	$C_{13}H_{15}FeN_6O_2$	21.28	20.95
Acetylisatin	224–226°	30	$C_{11}H_{10}N_6O_4$[a]	28.96	28.93
1-Benzylindole-3-carboxaldehyde	208–209°	91	$C_{17}H_{16}N_6O_2$	24.99	24.76
4-Bromobenzaldehyde	220–221°	92	$C_8H_8BrN_5O_2$	24.48	24.41
Cyclopentanone	139–141°	65	$C_6H_{11}N_5O_2$	37.82	37.74
Ferrocenecarboxaldehyde	195–196°	76	$C_{12}H_{13}FeN_6O_2$	22.23	22.05
4-Fluorobenzaldehyde	206–207°	83	$C_8H_8FN_5O_2$	31.10	30.94
Isatin	268–270°	98	$C_9H_8N_6O_3$[b]	33.86	33.87
Pentafluorobenzaldehyde	233–234°	94	$C_8H_4F_5N_5O_2$	23.57	23.41
Pyridine-3-carboxaldehyde	230–231°	67	$C_7H_8N_6O_2$	40.37	40.50
Quinoline-2-carboxaldehyde	228–229°	61	$C_{11}H_{10}N_6O_2$	32.55	32.40
3,4,5-Trimethoxybenzaldehyde	208–209°	76	$C_{11}H_{15}N_5O_5$	23.56	23.46

[a] Calc.: C, 45.52; H, 3.47. Found: C, 45.36; H, 3.61. [b] Calc.: C, 43.55; H, 3.25. Found: C, 43.68; H, 3.39.

Table III—4-Biphenylcarboxaldehyde Derivatives



RNH_2 Used	Melting Point	Yield, %	Formula	Analysis, % N Calc.	Analysis, % N Found
Diaminomaleonitrile	231–232°	83	$C_{17}H_{12}N_4$[a]	20.58	20.36
1,1-Dimethylhydrazine	86–87°	63	$C_{15}H_{16}N_2$	12.49	12.41
4-Phenylsemicarbazide	207–208°	95	$C_{20}H_{17}N_3O$	13.32	13.40
4-Phenyl-3-thiosemicarbazide	197–198°	99	$C_{20}H_{17}N_3S$	12.68	12.66

[a] Calc.: C, 74.98; H, 4.48. Found: C, 74.81; H, 4.35.

ketones (1) and showed antitubercular activity (2). Previously unreported compounds in these two series are shown in Tables II and III.

Screening results indicate a complete lack of antineoplastic activity (T/C of 125% for tumor survival systems and T/C 42% for tumor weight-inhibition systems) for all except the title compound in Tables II and III. Furthermore, of a large number of known nitroguanylhydrazones that have been screened, only three showed even marginal activity. KB cell culture activity was observed, however, in some of these compounds.

EXPERIMENTAL[1]

Nitroguanylhydrazones—To a warm solution of 1.19 g. (0.01 mole) of 1-amino-3-nitroguanidine in 10 ml. of ethanol, 10 ml. of water, and 20 ml. of acetic acid was added 0.01 mole of the carbonyl compound in 25 ml. of ethanol. The mixture was heated on the steam bath for 30 min., cooled, and filtered to give, after recrystallization from ethanol, the compounds listed in Table II.

4-Biphenylcarboxaldehyde Derivatives—To 1.82 g. (0.01 mole) of 4-biphenylcarboxaldehyde in 20 ml. of ethanol was added 0.01 mole of the appropriate carbonyl reagent in ethanol. The mixture was heated on the steam bath for 30 min., cooled, and filtered to give, after recrystallization from ethanol, the compounds listed in Table III.

[1] Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were determined in capillary tubes and are corrected.

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