stereochemistry of the heterocyclic derivatives at C-2 to be the same as the corresponding ketone, the hydrazines could have isomerized the methyl moiety during the condensation reaction. Use of semicarbazone or thiosemicarbazone resulted also in pyrazoles. All of the pyrazoles IIIa,c,d,f and VI exhibited uv maxima at 225–227 mμ, which shifted to 231–235 mμ in acidified alcohol. The phenylpyrazoles IIIb,e had a maximum at 253 mμ, which was not affected by acidification. No attempt was made to ascertain the exact location of the phenyl ring.

The pyrimidines IV were best prepared by melting an intimate mixture of the 1,3-diketones and guanidine carbonate or thiourea. Use of the standard base- or acid-catalyzed condensation conditions resulted only in the destruction or the recovery of diketone. The aminopyrimidines had double maxima of 230 and 303 mμ, which could be shifted by acid to 226 and 312 mμ, respectively. Thiourea product IVb had peaks at 233 and 286 mμ.

Preliminary evaluation of IIIa–e, IVd, V, and VI in the leukemia 1210 system[9] by single- and multiple-dose injections indicated the compounds to be neither active nor toxic. In the Walker 256 test system four doses of 400-mg total showed that IIIa,b decreased tumor weight only slightly.

Survey of a few representative compounds as IIId,e, and V in the paw edema antiinflammatory test and for androgenic–anabolic activity disclosed no significant activity.

Experimental Section

Pyrazole Formation.—The appropriate 1,3-diketone and $NH_2NH_2 \cdot H_2O$ or $C_6H_5NHNH_2$ (1 mol equiv) in EtOH (30–35 ml/g of diketone) was refluxed for 6 hr. The soln was cooled to 5° for 16 hr, and the product then collected. If insufficient product crystallized, the volume of EtOH was reduced *in vacuo* and additional material collected. The product was then recrystd from the appropriate solvent to give an analytical sample. Data for pyrazoles III and VI are listed in Table I.

TABLE I
DATA FOR NEW COMPOUNDS

Compd	Mp,[a] °C	Recrystn solvent[b]	Yield, %[c]	Formula	Analyses[d]
IIIa	254–255	A	89	$C_{13}H_{17}N_3O_2$	C, H, N
b	204–208	A	90	$C_{19}H_{21}N_3O_2$	C, H, N
c	199–202	B	60	$C_{15}H_{21}N_3O_2$	C, H, N
d	117–118	A	75	$C_{14}H_{19}N_3O_2$	C, H
e	190–192	A	62	$C_{20}H_{23}N_5O_2$	C, H, N
f	185–186	A	55	$C_{14}H_{19}N_3O_2$	C, H, N
IVa	255–257[e]	A	37	$C_{14}H_{18}N_4O_2$	N
b	260–265	C	69	$C_{14}H_{17}N_3O_2S$	N
c	198–200	A	24	$C_{16}H_{22}N_4O_2$	C, H, N
d	234–235	A	30	$C_{15}H_{20}N_4O_2$	N
V	119–120	D	20	$C_{12}H_{15}NO_4$	C, H, N
VI	233–236	A	57	$C_{12}H_{15}N_3O_2$	C, H, N

[a] Melting points were taken on a Fisher–Johns apparatus and are uncorrected. [b] A, EtOH; B, MeOH; C, H_2O; D, CH_2Cl_2. [c] Yields are based on material which could be crystallized directly from the reaction and had mp 0–4° lower than the analytical sample. [d] New compounds had the expected ir spectra. All analyses indicated by only the elemental symbol were within ±0.4% of the theoretical value. [e] A change in crystal structure occurs at 184–187°.

(9) We wish to thank Dr. H. B. Wood of the Drug Development Branch, Cancer Chemotherapy National Service Center for providing the anticancer assays.

Pyrimidine Formation.—An intimately ground mixture of diketone and guanidine carbonate or thiourea (1 mol equiv) was heated in an oil bath to 160–180°. The mixture liquified, then solidified upon continued heating. This change was accompanied by the release of H_2O vapor. The solid was added to a few milliliters of boiling H_2O to remove the unreacted urea. After collecting the H_2O treated product, it was recrystd from EtOH or H_2O to give the desired pyrimidine. Yields and physical data for the pyrimidines IV are in Table I.

Halogenated 1-(4-Aminobenzylidene)indenes[1,2]

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1-(4-Dimethylaminobenzylidene)indene (I) and a number of its analogs have been found active against subcutaneous Walker 256 tumors, intramuscular Walker 256 tumors, and Lymphoma 8.[3,4,5] Moreover, I appeared to cause mammary tumors, especially in female rats. In order to determine whether halogen atoms *ortho* to the amino group would reduce the carcinogenic activity, we have prepared the compounds listed in Table I and submitted then for testing. The results obtained indicate that most of the *ortho*-halogenated compounds have activity against the Walker tumors in one or both types of test. Some of the compounds seem more effective in the single dose test, possibly because they are slower in absorption or activation than the unhalogenated compounds. When compared on a molar basis the bromo compounds appeared to be somewhat more effective than the fluoro, chloro, or iodo compounds. It is interesting to note that the *m*-chloro compound was inactive. A similar effect of a halogen atom in this position has been observed in the 4-(4-dimethylaminostyryl)quinoline series. A halogen atom at the 2 or 3 position of the indene portion of the molecule also prevented antitumor activity.

Base-catalyzed condensation of the halogenated aminobenzaldehyde with indene seemed to go smoothly, but isolation and purification of the desired products required patient attention, as did preparation of the halogenated aldehydes.

Experimental Section

Equal molar quantities of aldehyde and indene were dissolved separately in hot EtOH and then combined in preparing the halogenated 1-(4-aminobenzylidene)indenes. After KOH in EtOH was added dropwise in excess until a color change occurred, the solution was allowed to reflux about 30 min, then cooled, and filtered.

3-Fluoro-4-dimethylaminobenzaldehyde was prepared from *N*,*N*-dimethyl-*o*-fluoroaniline according to the method of Campaigne and Archer.[6] 3-Chloro-4-dimethylaminobenzaldehyde

(1) This investigation was supported by Public Health Service Research Grants No. CA-03717-07, -10, and -11 from the National Cancer Institute.

(2) Presented at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., December 6, 1968.

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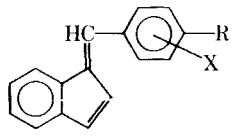
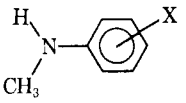
TABLE I: 1-(4-AMINOBENZYLIDENE)INDENES



						Single dose[d]				Multiple dose[e]			
						Effect (tumor wt)		Lethality		Effect (tumor wt)		Lethality	
R	X	Yield, %	Mp, °C[a]	Recrystn[b] solvent	Formula[c]	mg/kg	T/C	mg/kg	No. killed	mg/kg (× 4)	T/C	mg/kg (× 4)	No. killed
$N(CH_3)_2$	H					50	0.25	1600	0/3	100	0.18	600	0/6
						100	0	2000	3/3	1600	0	1600	4/18
$N(CH_3)_2$	3-F	33	83–84[f,m]	E, I	$C_{18}H_{16}FN$					100	0.52	600	0/6
										600	0.15		
$N(CH_3)_2$	2-Cl	67	139.0–139.5	aE, I	$C_{18}H_{16}ClN$	400	1.43	1600	0/3				
						1600	1.00						
$N(CH_3)_2$	3-Cl	16	78[h]	I, E	$C_{18}H_{16}ClN$					400	0.36	400	1/14
$N(CH_3)_2$	3-Br	59	95–96	I, E	$C_{18}H_{16}BrN$	200	0.11	1600	0/3	400	0.29	400	0/6
						1600	0						
$NHCH_3$	H					10	0.25	40	0/3	25	0.58	100	0/6
						80	0	80	1/3	100	0.20	200	5/6
$NHCH_3$	3-Cl	48	82.8–83.2	I, E	$C_{17}H_{14}ClN$					100	0.53	400	0/6
										400	0.24		
$NHCH_3$	3-Br	53	92–93[i,j]	I, E	$C_{17}H_{14}BrN$	100	0.06	250	0/3	50	0.54	600	0/6
						250	0.01	625	5/5	600	0.06		
$NHCH_3$	3-I	45	140–141[k]	I, O, aE	$C_{17}H_{14}IN$	320	0.08	1280	0/3	400	1.04	400	0/6
						1280	0						
$NHCH_3$	3,5-Cl_2	27	119.0–120.0[l,m]	I, E	$C_{17}H_{13}Cl_2N$					400	0.92	400	0/6
$NHCH_3$	3,5-Br_2	25	100.5–101.5[l,n]	I, E	$C_{17}H_{13}Br_2N$	200	0.50	1250	0/3	400	0.81	400	0/6
						1250	0.20						
NH_2						40	0	125	1/2	9.4	0.33	37.5	0/6
						80	0	160	2/3	37.5	0.18	75	4/6
NH_2	3,5-Cl_2	31	135.0–135.6[o]	I, E	$C_{17}H_{13}Cl_2N$	20	0.62	50	0/3	400	0.62	400	0/6
								125	3/5				
NH_2	3,5-Br_2	57	165–166[o]	O, aE	$C_{17}H_{13}Br_2N$	20	0.53	50	0/3				
1-(4-Dimethylaminobenzylidene)-2-chloroindene		34	136–137[k]	P, I	$C_{18}H_{16}ClN$	400	0.72	400	0/3				
						1600	0.62	1600	0/3				
1-(4-Dimethylaminobenzylidene)-3-bromoindene		29	152–154[k]	I	$C_{18}H_{16}BrN$	800	0.83	800	0/3				

[a] Determined with Mel-Temp melting point apparatus. [b] aE, absolute EtOH; E, 95% EtOH; I, mixed isomeric branched hexanes (isohexanes); O, mixed branched isomeric octanes (isooctanes). [c] All compounds were analyzed for C and H by Galbraith Laboratories except where indicated otherwise. Analytical results obtained for those elements were within 0.3% of the theoretical values. [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 interperitoneal 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 and the average weights of tumors in treated and untreated hosts are reported as the ratio T/C. [e] We are grateful to CCNSC for screening tests against Walker 256 in random bred albino rats, using four daily interperitoneal injections in CMC or peanut oil administered beginning 3 days after implantation; rats were sacrificed 7 days after implantation. [f] All compounds are yellow except where indicated otherwise. [g] Recrystallized from isohexanes, dissolved in C_6H_6, chromatographed on Bio-Sil A 200-325 mesh silica gel, and eluted with C_6H_6. [h] Reaction mixture flash evaporated under vacuum, the resulting residue dissolved in C_6H_6, and chromatographed on alumina and/or silica gel. [i] Red–orange. [j] Mother liquor flash evaporated under vacuum, the residue dissolved in C_6H_6 and chromatographed on alumina; product obtained from yellow band which formed when the column was eluted with C_6H_6. [k] Red. [l] Yellow orange. [m] Recrystallized from isohexane and twice from 95% EtOH, dissolved in C_6H_6, chromatographed on Bio Sil A 200–325 mesh silica gel, eluted with C_6H_6. [n] A minimum amount of alcoholic KOH was used, and the reaction was refluxed for 10 min and allowed to cool; resulting oil dissolved in C_6H_6 and chromatographed on alumina. [o] Recrystallized from isohexanes, and 95% EtOH; dissolved in 3:1 isohexane–C_6H_6, chromatographed on 60–200 mesh silica gel, and eluted with 3:1 isohexane–C_6H_6. [p] Extracted with isohexane and 95% EtOH, resulting crystals dissolved in C_6H_6 and chromatographed on silica gel, and product obtained from the first C_6H_6 fraction.

TABLE II
4-METHYLAMINOBENZALDEHYDES



X	Yield, %	Mp, °C[a]	Crystn solvent[b]	Formula[c]
3-Br	61	75.0–76.0[d]	I, IE	C_8H_8BrNO
3-I	44	81.0–82.0[e]	IE	C_8H_8INO[f]
3,5-Br_2	60	73.0–73.5	I	$C_8H_7Br_2NO$
3,5-Cl_2	12	85.0–85.6	I, IE	$C_8H_7Cl_2NO$

[a] Determined with Mel-Temp melting point apparatus. [b] I, mixed isomeric branched hexanes; IE, *i*-Pr_2O. [c] All compounds were analyzed for C and H by Galbraith Laboratories except where indicated otherwise; analytical results were within ±0.3% of the theoretical values. [d] Reaction mixture was stirred 10 min and poured into 1300 ml of H_2O; a few g of $NaHSO_3$ in H_2O were added, the mixture was filtered and washed repeatedly with H_2O. [e] Isooctane extractions treated with sodium thiosulfate and concentrated to obtain additional material. [f] Not analyzed.

was prepared by reacting *t*-BuOCl with 4-dimethylaminobenzaldehyde.[7] 2-Chloro- and 3-bromo-4-dimethylaminobenzaldehyde were prepared by the halogenation of 4-dimethylaminobenzaldehyde according to the method of Brady and Truskowski,[8] but using an equivalent amount of NaOAc in the reaction. The 3-chloro-, 3-bromo-, 3,5-dichloro-, and 3,5-dibromo-4-methylaminobenzaldehydes were prepared similarly. In making the 3-chloro compound most of the AcOH was evaporated under vacuum, and the remaining material poured into 2 l. of H_2O and neutralized with $NaHCO_3$. The resulting oil and/or ppt was dissolved in C_6H_6 and chromatographed on silica gel. During elution with C_6H_6 the 3,5-dichloro compound passed through first, and then the 3-chloro derivative. The 3,5-dichloro compound, however, was obtained principally using 2 equiv of Cl_2/equiv of aldehyde and stirring the reaction mixture for 2 hr. 3-Iodo-4-methylaminobenzaldehyde was prepared by adding 24.2 g of ICl dropwise with stirring to 20 g (0.148 mol) of 4-methylaminobenzaldehyde in 70 ml of AcOH at 12–25°. After standing 3 hr the mixture was hydrolyzed over ice and neutralized with NaOH and $NaHCO_3$. 4-Amino-3,5-dichlorobenzaldehyde was obtained by adding dropwise a solution of Cl_2 in AcOH to a dilute AcOH solution of the HCl salt of 4-aminobenzaldehyde. The product was obtained according to the method of van de Bunt.[9] 4-Amino-3,5-dibromobenzaldehyde was prepared from 3-bromo-4-dimethylaminobenzaldehyde perbromide hydrochloride.[10,11]

1-(3-Chloro-4-dimethylaminobenzylidene)-3-(α-hydroxy-3-chloro-4-dimethylaminobenzyl)indene [isolated and analyzed as the dipicrate (*Anal.* ($C_{49}H_{42}Cl_2N_8O_{15}$) C, H, Cl; H: calcd, 3.49; found, 4.04)] and **1**-(3,5-dibromo-4-methylaminobenzylidene)-3-(α-hydroxy-3,5-dibromo-4-methylaminobenzyl)indene (*Anal.* ($C_{25}H_{20}Br_4N_2O$) C, H) were obtained as by-products in the preparation of **1**-(3-chloro-4-dimethylaminobenzylidene)indene and **1**-(3,5-dibromo-4-methylaminobenzylidene)indene, respectively.

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Synthesis and Alkylation of Tetrahydrocyclopentapyrazolols

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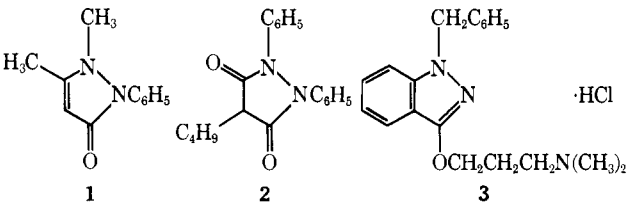
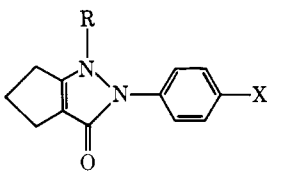
Antipyrine (**1**) has long been recognized as an analgetic–antipyretic agent;[1] phenylbutazone (**2**) has become a widely used analgetic–antiinflammatory drug;[1] and benzydamine (**3**) has received notice as a potentially useful analgetic–antiinflammatory agent in man.[1,2] Although in many ways dissimilar, certain structural features common to **1**, **2**, and **3** may be

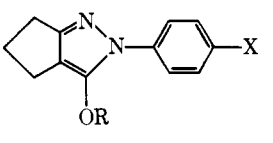


1 **2** **3**

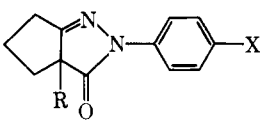
recognized. Each compound possesses an oxygen-bearing pyrazole heterocycle which supports an aryl or alkyl N substituent and a C substituent. The tetrahydrocyclopentapyrazolones **4**, **5**, and **6**, synthesized by Mannich in 1929,[3,4] combine these structural units in a different manner. We undertook to repeat this work, and to prepare a brief series of analogs for examination in an antiinflammatory screening program.



4, R = X = H
5, R = H; X = Br
6, R = CH_3; X = H
7, R = $CH_2CH{=}CH_2$; X = H
8, R = $CH_2C_6H_5$; X = Br
9, R = $CH_2C_6H_5$; X = F



10, R = X = H
11, R = H; X = Br
12, R = H; X = F
13, R = CH_3; X = H
14, R = $CH_2C_6H_5$; X = F



15, R = H; X = H
16, R = H; X = Br
17, R = H; X = F
18, R = CH_3; X = H
19, R = $CH_2CH{=}CH_2$ X = H
20, R = $CH_2C_6H_5$; X = Br
21, R = $CH_2C_6H_5$; X = F

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