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Synthesis and Analgesic Effect of *N*-Substituted 5-Arylidene-6-methyl-3-(4*H*)-pyridazinones

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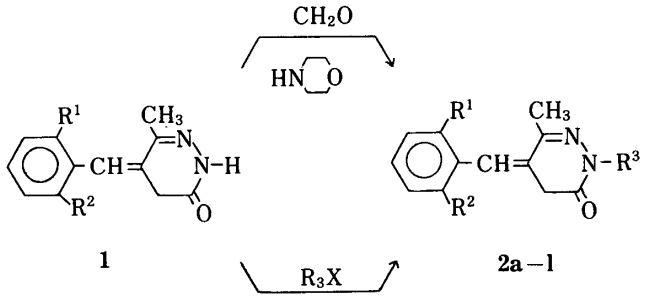
Two methods of *N*-substitution were applied to 5-arylidene-6-methyl-3-(4*H*)-pyridazinones. The resulting derivatives were tested in order to determine the area of pharmacological activity. Most compounds exhibited a dose-dependent analgesic activity. Introduction of a benzoyl substituent in the 2-position of the pyridazinone ring **2j** induced the most potent activity.

Keywords——arylidene-pyridazinone; *N*-aminoalkylpyridazinone; *N*-alkylpyridazinone; *N*-aroylpyridazinone; analgesic activity; anti-inflammatory activity

Various derivatives containing a 3-(2*H*)-pyridazinone ring have been described. Recently, it was reported that *N*-substituted pyridazinones show antiulcer,[1] analgesic and anti-inflammatory[2,3] activities. In our search for new analgesic and anti-inflammatory agents, we synthetized a number of new pyridazinone derivatives. We found that some of them were active as analgesic compounds.

Results and Discussion

The 5-arylidene-6-methyl-2-substituted-3-(4*H*)-pyridazinones listed in Table I were prepared according to the following scheme:



5-Arylidene-6-methyl-3-(4*H*)-pyridazinones (**1**) were synthesized by a method described in previous papers.[4,5] Compound **2a** was obtained through a Mannich reaction. Compounds **2b** to **2l** were prepared by alkylation or acylation procedures. All compounds were evaluated for analgesic activity as described in the experimental section. Physical and pharmacological data are summarized in Table I; spectral data are reported in Table II.

Behavioral effects and oral acute toxicity were first investigated in mice. No significant behavioral effects were observed even at doses up to 800 mg/kg *p.o.* With such doses, all animals were still alive after an observation period of one week. A number of derivatives showed a good dose-dependent activity in the phenylquinone-induced writhing test in mice

TABLE I. Physical Constants and Analgesic Activity of 2-Substituted Pyridazinones **2** at 25, 50 and 100 mg/kg

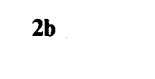
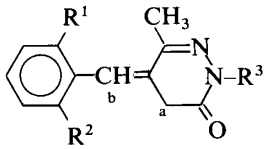
Compd. No.	R^1	R^2	R^3	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Cl	Analgesic activity (%) 25	50	100 (mg/kg)
2a	H	H		69	80	$C_{17}H_{21}N_3O_2$	68.23 (68.51	7.02 7.23	10.70 10.84)		25.4±5.7	34.6±6.6	39.8±5.5
2b	H	H		96	226	$C_{16}H_{22}ClN_3O$	62.44 (62.23	7.16 7.18	13.66 13.56	11.54 11.37)	16.2±3.9	42.4±5.8	56.3±6.8
2c	H	H		93	200	$C_{18}H_{24}ClN_3O_2$	61.80 (61.78	6.87 6.82	12.02 12.02	10.15 10.92)	26.7±5.7	25.1±4.0	13.6±2.5
2d	Cl	H		89	204	$C_{18}H_{23}Cl_2N_3O_2$	56.25 (55.98	5.99 5.95	10.94 10.42	18.49 18.67)	6.8±1.5	5.0±1.9	2.3±0.8
2e	Cl	Cl		60	220	$C_{18}H_{22}Cl_3N_3O_2$	51.61 (51.12	5.26 5.24	10.04 9.84	25.45 25.79)	30.4±5.9	32.5±5.2	48.2±4.3
2f	H	H	CH_2–C_6H_5	79	88	$C_{19}H_{18}N_2O$	78.62 (78.01	6.21 6.28	9.65 9.80)		31.7±4.9	39.0±5.6	47.4±3.9
2g	H	H	$(CH_2)_2$–C_6H_5	53	86	$C_{20}H_{20}N_2O$	78.95 (78.15	6.58 6.53	9.21 9.29)		15.9±4.6	29.3±5.7	50.3±5.7
2h	H	H	$(CH_2)_3$–C_6H_5	31	52	$C_{21}H_{22}N_2O$	79.25 (79.48	6.92 6.96	8.80 8.52)		17.3±6.0	23.8±3.9	44.2±4.7
2i	H	H	$CH(CH_3)$–CO–C_6H_5	15	96	$C_{21}H_{20}N_2O_2$	75.90 (76.01	6.03 5.99	8.43 8.20)		9.7±2.0	24.6±4.7	29.3±2.9
2j	H	H	CO–C_6H_5	21	92	$C_{19}H_{16}N_2O_2$	75.00 (74.81	5.26 5.24	9.21 9.06)		25.4±3.7	35.9±5.2	68.3±3.9
2k	Cl	H	CO–C_6H_5	17	112	$C_{19}H_{15}ClN_2O_2$	67.36 (67.15	4.43 4.53	8.27 8.12	10.49 10.46)	13.4±2.9	23.6±5.8	54.5±5.2
2l	Cl	Cl	CO–C_6H_5	16	190	$C_{19}H_{14}Cl_2N_2O_2$	61.13 (61.19	3.75 3.74	7.51 7.52	19.03 19.11)	5.2±1.7	20.1±3.3	33.8±4.9
1a	H	H	H	80	176	$C_{12}H_{12}N_2O$					1.6±0.5	3.9±1.4	7.6±3.0
Aspirin											25.9±4.0	52.4±3.6	77.7±3.9
Noramidopyrine											24.6±3.1	39.3±5.0	90.8±3.9

TABLE II. Spectral Data for 2-Substituted Pyridazinones **2**



Compd. No.	R^1	R^2	R^3	IR ν (cm^{-1}) KBr	^{1}H-NMR Chemical shift (δ, in $CDCl_3$)
2a	H	H	CH_2(c)–N(O)(e f)	1660 1600 1570	2.25 (s, 3H, CH_3), 2.75 (m, 4H, e), 3.70 (m, 4H, f), 3.80 (s, 2H, a), 5.00 (s, 2H, c), 6.60 (s, 1H, b), 7.35 (m, 5H, Ar)
2b	H	H	CH_2(c)–CH_2(d)–$N^+H(CH_3)_2$(e)·Cl^-	2500 1660 1600 1580	2.20 (s, 3H, CH_3), 2.90 (s, 6H, e), 3.50 (t, 2H, d), 3.80 (s, 2H, a), 4.50 (t, 2H, c), 6.50 (s, 1H, b), 7.30 (m, 5H, Ar), 12.50 (s, 1H, NH^+)
2c	H	H	CH_2(c)–CH_2(d)–N^+H(O)(e f)·Cl^-	2400 1670 1600 1580	2.20 (s, 3H, CH_3), 3.10 (m, 2H, d), 3.50 (m, 4H, e), 3.80 (s, 2H, a), 4.10 (m, 4H, f), 4.60 (t, 2H, c), 6.50 (s, 1H, b), 7.30 (m, 5H, Ar), 13.00 (s, 1H, NH^+)
2d	Cl	H	CH_2(c)–CH_2(d)–N^+H(O)(e f)·Cl^-	2550 1680 1610 1590	2.35 (s, 3H, CH_3), 3.15 (m, 2H, d), 3.50 (t, 4H, e), 3.90 (s, 2H, a), 4.15 (m, 4H, f), 4.65 (t, 2H, c), 6.35 (s, 1H, b), 7.35 (m, 4H, Ar), 13.30 (s, 1H, NH^+)
2e	Cl	Cl	CH_2(c)–CH_2(d)–N^+H(O)(e f)·Cl^-	2550 1670 1600 1580	2.45 (s, 3H, CH_3), 3.15 (m, 2H, d), 3.55 (m, 4H, e), 4.10 (s, 2H, a), 4.25 (m, 4H, f), 4.65 (m, 2H, c), 6.10 (s, 1H, b), 7.35 (m, 4H, Ar), 12.80 (s, 1H, NH^+)
2f	H	H	CH_2(c)–C_6H_5	1660 1600 1580	2.35 (s, 3H, CH_3), 3.75 (s, 2H, a), 3.95 (s, 2H, c), 6.65 (s, 1H, b), 7.35 (m, 5H, Ar), 7.45 (m, 5H, C_6H_5)
2g	H	H	CH_2(c)–CH_2(d)–C_6H_5	1660 1600 1590	2.25 (s, 3H, CH_3), 3.20 (t, 2H, c), 3.85 (s, 2H, a), 4.40 (t, 2H, d), 6.60 (s, 1H, b), 7.35 (m, 5H, Ar), 7.45 (m, 5H, C_6H_5)
2h	H	H	CH_2(c)–CH_2(d)–CH_2(e)–C_6H_5	1660 1600 1580	2.15 (m, 2H, d), 2.30 (s, 3H, CH_3), 2.80 (t, 2H, e), 3.85 (s, 2H, a), 4.25 (t, 2H, c), 6.55 (s, 1H, b), 7.30 (m, 5H, Ar), 7.40 (m, 5H, C_6H_5)
2i	H	H	CH(c)(CH_3)(d)–CO–C_6H_5	1695 1660 1595 1580	1.65 (d, 3H, d), 2.15 (s, 3H, CH_3), 3.75 (s, 2H, a), 6.35 (m, 1H, c), 6.55 (s, 1H, b), 7.35 (m, 5H, Ar), 8.00 (m, 5H, C_6H_5)
2j	H	H	CO–C_6H_5	1740 1670 1600 1580	2.25 (s, 3H, CH_3), 4.00 (s, 2H, a), 6.60 (s, 1H, b), 7.35 (m, 5H, Ar), 7.70 (m, 5H, C_6H_5)
2k	Cl	H	CO–C_6H_5	1730 1670 1610 1590	2.40 (s, 3H, CH_3), 4.15 (s, 2H, a), 6.35 (s, 1H, b), 7.35 (m, 5H, Ar), 7.70 (m, 5H, C_6H_5)
2l	Cl	Cl	CO–C_6H_5	1725 1660 1590 1580	2.50 (s, 3H, CH_3), 4.15 (s, 2H, a), 6.15 (s, 1H, b), 7.35 (m, 5H, Ar), 7.80 (m, 5H, C_6H_5)

treated orally. The compounds **2b**, **g**, **j**, **k** exhibited remarkable activities as shown in Table I. Considering structure-activity relationships, it is interesting that **2j** and **2k** showed higher analgesic activities than did **2i** containing and additional carbon at the 2-position. Moreover, introduction of a chlorine atom on the phenyl nucleus in the 5-position did not enhance analgesic activity. The active compounds in the above assay were submitted to further pharmacological tests, such as the hot plate test[6,7] and carrageenin-induced edema test in rats treated orally.[8,9] However, only a weak anti-inflammatory activity was detected in the pyridazinone **2b**.

In conclusion, several compounds were found to possess a significant dose-dependent analgesic activity. The substitution of the pyridazinone ring was therefore advantageous for activity in comparison with unsubstituted pyridazinones **1**, which have no analgesic activity.

Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Beckman 4240 spectrophotometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM 360 A spectrometer. Resonance positions are given on the δ scale (parts per million) relative to internal tetramethylsilane. The NMR signals were designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet.

Chemistry——5-Benzylidene-6-methyl-2-morpholinomethyl-(4*H*)-3-pyridazinone (**2a**): A solution of 35% aqueous formaldehyde (1.7 ml, 0.02 mol) was added to morpholine (1.74 g, 0.02 mol) with continuous stirring. Then the solution was heated to 60 °C and benzylidenepyridazinone **1** (4 g, 0.02 mol), acetic acid (1.2 g, 0.02 mol) and ethanol (10 ml) were added. The mixture was refluxed for 6 h and evaporated *in vacuo*. The residue was neutralized with 20% aqueous sodium hydroxide and extracted with diethyl ether. The combined extracts were dried on sodium sulfate and evaporated *in vacuo*. The residue was triturated with diisopropyl ether and the solid which was formed, was collected by filtration and dried.

5-Arylidene-6-methyl-2-(β-alkylaminoethyl)-(4*H*)-3-pyridazinones Hydrochlorides (**2b—e**): The appropriate pyridazinone **1** (0.02 mol) was added to an ethanolic solution (50 ml) of sodium (0.46 g, 0.02 g atom). On the other hand, a solution of a 2-chloroethylamine hydrochloride (0.02 mol) in absolute ethanol (40 ml) was added to an ethanolic solution (50 ml) of sodium (0.46 g, 0.02 g atom). The two solutions were mixed and stirred at room temperature for 1 h. Afterwards, the mixture was heated to 50 °C for 2 h and then refluxed for 8 h. The cooled suspension was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in absolute ethanol (20 ml) and the solution was saturated with gaseous hydrochloric acid. Compounds **2b—e** were precipitated by addition of diethyl ether and recrystallized from ethanol.

5-Benzylidene-6-methyl-2-phenylalkyl-(4*H*)-3-pyridazinones (**2f—i**): Potassium hydroxide (1.12 g, 0.02 mol) and *N*-tetrabutylammonium bromide (0.76 g, 0.002 mol) were added to a solution of benzylidene pyridazinone **1** (4 g, 0.02 mol) and phenylalkyl bromide (0.02 mol) in benzene (100 ml). The mixture was stirred and refluxed for 18 h. After evaporation the residue was triturated with diisopropyl ether. The crude product was chromatographed on silica gel (ethyl acetate) and recrystallized from ethanol.

5-Arylidene-6-methyl-2-benzoyl-(4*H*)-3-pyridazinones (**2j—l**): Benzoyl chloride (3.37 g, 0.02 mol) was added dropwise in an ice bath to a solution of an arylidenepyridazinone **1** (0.02 mol) in anhydrous pyridine (80 ml). The solution was stirred overnight at room temperature and refluxed for 5 h. After evaporation, the residue was triturated with diisopropyl ether. The crude product was chromatographed on silica gel (ethyl acetate) and recrystallized from ethanol.

Pharmacology——All compounds were administered orally in a 0.5% hydroxypropyl methyl cellulose suspension to Iffa Credo OF_1 male mice (20 g).

Behavioral Effects and Acute Toxicity in Mice: The compounds were administered at various doses. The animals were observed over 24 h and the symptomatology was noted. In addition, they were kept under observation for 8 d to detect any sign of toxicity.

Phenylquinone Writhing Test[10,11]: Groups of five mice were given i.p. a 0.02% solution (ethanol–water, 5 : 95) of phenylquinone (P.B.Q) 30 min after oral administration of test drugs. The writhing response frequency of each animal was counted between the 5 th and the 15 th min after the injection of the irritant agent.

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References and Notes

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