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Antidepressant Activity of New 3-Amino-5-disubstituted Benzylidene-6-methyl-(4*H*)-pyridazine Derivatives

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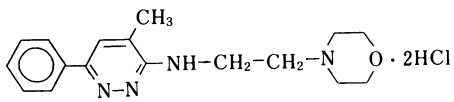
By the reaction of various amines with 3-chloropyridazines, several minaprine analogues were prepared. Most of them exhibited significant antidepressant activity. Compound **2a** antagonizes reserpine action and neuroleptic-induced catalepsy in a dose-dependent manner.

Keywords——disubstituted benzylidene pyridazine; 3-amino pyridazine derivative; minaprine analogue; antidepressant activity

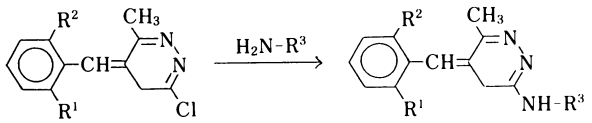
Recently, it was reported that minaprine proved to be effective in the treatment of various depressive disorders.[1] This 3-amino-6-phenylpyridazine derivative is known to represent a new class of psychotropic drugs.[2] This prompted us to synthesize analogues containing a 5-disubstituted benzylidene pyridazine moiety. Most of them were found to be effective in antidepressant activity tests.



minaprine

Results and Discussion

The selected compounds were synthesized according to the scheme shown.



1 **2a–g**

3-Chloro-5-disubstituted benzylidene-6-methyl-4*H*-pyridazines (**1**) were prepared as described in a previous paper.[3] They were refluxed with an excess of the requisite amine to afford 3-amino-5-disubstituted benzylidene-6-methyl-4*H*-pyridazine derivatives (**2a—g**). All compounds were evaluated for antidepressant activity as described in the experimental section. Physical and spectral data are summarized in Tables I and II: pharmacological data are reported in Table III.

TABLE I. Physical Constants of 3-Amino Pyridazine Derivatives **2**

Compd.	R^1	R^2	R^3	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	Cl	N
2a	H	Cl	$CH_2-CH_2-N(CH_3)_2\cdot 2H_2O$	38	65	$C_{16}H_{25}ClN_4O_2$	56.39	7.34	10.43	16.44
							(56.09	7.08	10.54	16.32)
2b	Cl	Cl	$CH_2-CH_2-N(CH_3)_2$	71	142	$C_{16}H_{20}Cl_2N_4$	56.64	5.90	20.94	16.52
							(56.61	5.84	20.92	16.67)
2c	H	H	$CH_2-CH_2-CH_2-N(CH_3)_2$	69	122	$C_{17}H_{24}N_4$	71.83	8.45		19.72
							(71.69	8.49		19.46)
2d	Cl	Cl	$CH_2-CH_2-CH_2-N(CH_3)_2\cdot 2H_2O$	57	116	$C_{17}H_{26}Cl_2N_4O_2$	52.44	6.68	18.25	14.40
							(52.56	6.41	18.38	14.34)
2e	H	H	$CH_2-CH_2-N\langle O \rangle$	68	142	$C_{18}H_{24}N_4O$	69.23	7.69		17.95
							(69.46	7.60		17.60)
2f	H	Cl	$CH_2-CH_2-N\langle O \rangle$	55	124	$C_{18}H_{23}ClN_4O$	62.34	6.64	10.24	16.16
							(62.55	6.53	10.23	16.41)
2g	Cl	Cl	$CH_2-CH_2-N\langle O \rangle$	51	164	$C_{18}H_{22}Cl_2N_4O$	56.69	5.77	18.64	14.70
							(56.46	5.96	18.68	14.58)

TABLE II. Spectral Data for 3-Amino Pyridazine Derivatives **2**

Compd.	R^1	R^2	R^3	IR ν (cm^{-1}) KBr	^{1}H-NMR Chemical shift (δ) (in DMSO-d_6)
2a	H	Cl	$\overset{c}{CH_2}-\overset{d}{CH_2}-N(\overset{e}{CH_3})_2\cdot 2H_2O$	3300 1620 1570	2.10 (s, 6H, e), 2.40 (m, 2H, d), 2.45 (s, 3H, CH_3), 3.35 (m, 2H, c), 3.40 (s, 4H, $2H_2O$), 3.90 (s, 2H, a), 6.10 (s, 1H, b), 6.30 (br s, 1H, NH), 7.40 (m, 4H, Ar)
2b	Cl	Cl	$\overset{c}{CH_2}-\overset{d}{CH_2}-N(\overset{e}{CH_3})_2$	3260 1620 1570	2.10 (s, 6H, e), 2.30 (m, 2H, d), 2.50 (s, 3H, CH_3), 3.40 (m, 2H, c), 4.10 (s, 2H, a), 6.00 (s, 1H, b), 6.30 (br s, 1H, NH), 7.50 (m, 3H, Ar)
2c	H	H	$\overset{c}{CH_2}-\overset{d}{CH_2}-\overset{e}{CH_2}-N(\overset{f}{CH_3})_2$	3250 1630 1570	1.70 (m, 2H, d), 2.20 (s, 6H, f), 2.30 (m, 2H, e), 2.35 (s, 3H, CH_3), 3.20 (m, 2H, c), 3.80 (s, 2H, a), 6.50 (s, 1H, b), 6.70 (br s, 1H, NH), 7.20 (m, 5H, Ar)
2d	Cl	Cl	$\overset{c}{CH_2}-\overset{d}{CH_2}-\overset{e}{CH_2}-N(\overset{f}{CH_3})_2\cdot 2H_2O$	3260 1620 1580	1.80 (m, 2H, d), 2.10 (s, 6H, f), 2.30 (m, 2H, e), 2.40 (s, 3H, CH_3), 3.20 (m, 2H, c), 3.40 (s, 4H, $2H_2O$), 4.00 (s, 2H, a), 5.70 (br s, 1H, NH), 6.40 (s, 1H, b), 7.30 (m, 3H, Ar)
2e	H	H	$\overset{e}{CH_2}-\overset{d}{CH_2}-N\langle \overset{f}{O} \rangle$	3240 1615 1575	2.30 (m, 2H, d), 2.40 (s, 3H, CH_3), 2.50 (m, 4H, e), 3.45 (m, 2H, c), 3.70 (m, 4H, f), 3.80 (s, 2H, a), 5.05 (br s, 1H, NH), 6.25 (s, 1H, b), 7.25 (m, 5H, Ar)
2f	H	Cl	$\overset{c}{CH_2}-\overset{d}{CH_2}-N\langle \overset{f}{O} \rangle$	3300 1615 1590	2.40 (m, 2H, d), 2.50 (s, 3H, CH_3), 2.60 (m, 4H, e), 3.60 (m, 2H, c), 3.70 (m, 4H, f), 4.00 (s, 2H, a), 5.10 (br s, 1H, NH), 6.10 (s, 1H, b), 7.30 (m, 4H, Ar)
2g	Cl	Cl	$\overset{c}{CH_2}-\overset{d}{CH_2}-N\langle \overset{f}{O} \rangle$	3260 1630 1570	2.30 (m, 2H, d), 2.40 (s, 3H, CH_3), 2.50 (m, 4H, e), 3.50 (m, 2H, c), 3.60 (m, 4H, f), 4.10 (s, 2H, a), 5.90 (br s, 1H, NH), 6.40 (s, 1H, b), 7.40 (m, 3H, Ar)

The experimental study on animals indicated that most derivatives antagonized reserpine-induced ptosis as well as prochlorperazine-induced catalepsy. Compounds **2a**, **2c**, **2f** exhibited remarkable activities as shown in Table III. They antagonized reserpine-induced ptosis in a dose-dependent manner, in the range of 25 to 100 mg/kg. Maximal antagonism of ptosis was achieved 1 h after reserpine administration. Four hours after treatment, all

TABLE III. Pharmacological Data for 3-Amino Pyridazine Derivatives **2**

Compd.	Dose (mg/kg) *p.o.*	Antagonism of reserpine-induced ptosis Percentage of protection			Antagonism of prochlorperazine-induced catalepsy Percentage of noncataleptic rats 5 h after treatment
		1 h after treatment	2 h after treatment	4 h after treatment	
2a	25	54 ± 10[a]	25 ± 9[a]	8 ± 7 (NS)	63[a]
	50	61 ± 8[a]	33 ± 9[a]	17 ± 8[b]	71[a]
	100	72 ± 12[a]	47 ± 1[a]	25 ± 9[a]	82[a]
2b	25	20 ± 8[b]	11 ± 5[b]	8 ± 6 (NS)	32[c]
	50	28 ± 9[a]	19 ± 7[a]	13 ± 7[b]	40[b]
	100	40 ± 10[a]	32 ± 8[a]	20 ± 10[b]	51[a]
2c	25	25 ± 10[a]	21 ± 9[a]	4 ± 3 (NS)	25[b]
	50	42 ± 11[a]	31 ± 9[a]	7 ± 5 (NS)	38[a]
	100	63 ± 11[a]	49 ± 10[a]	17 ± 8[b]	63[a]
2d	25	40 ± 11[a]	24 ± 6[a]	5 ± 5 (NS)	18 (NS)
	50	47 ± 12[a]	33 ± 6[a]	17 ± 9[b]	33[c]
	100	58 ± 9[a]	42 ± 9[a]	25 ± 11[a]	42[b]
2e	25	9 ± 7 (NS)	5 ± 4 (NS)	2 ± 2 (NS)	11 (NS)
	50	15 ± 8[b]	8 ± 6 (NS)	4 ± 3 (NS)	30[c]
	100	24 ± 9[b]	14 ± 5[b]	11 ± 5[b]	59[a]
2f	25	44 ± 9[a]	18 ± 7[a]	12 ± 6[b]	30[c]
	50	58 ± 9[a]	24 ± 9[a]	16 ± 8[a]	60[a]
	100	70 ± 12[a]	40 ± 9[a]	29 ± 9[a]	75[a]
2g	25	34 ± 10[a]	20 ± 8[a]	10 ± 5[c]	20 (NS)
	50	41 ± 7[a]	24 ± 8[a]	18 ± 6[a]	30[c]
	100	50 ± 12[a]	39 ± 9[a]	21 ± 8[a]	35[c]
Minaprine	25	51 ± 8[a]	42 ± 8[a]	29 ± 8[a]	72[a]

The level of significance was *a*) $p<0.01$, except: *b*) $0.02<p<0.05$; *c*) $0.01<p<0.02$; NS, not significant.

compounds failed to antagonize reserpine-induced ptosis even at doses of 100 mg/kg. The nature and the length of the amino-chain at the 3-position on the pyridazine ring did not have a clear influence in terms of the pharmacological data. Compounds **2a**—**d** with a dimethylamino group were not significantly more potent than compounds **2e**—**g** containing a morpholino group. In the same way, compounds **2a**, **2b** and compounds **2c**, **2d** with an additional carbon on the alkylamino chain did not present significant different activities. In addition, the presence of one chlorine atom on the phenyl nucleus in the case of compounds **2a** and **2f** seemed to be favorable for antidepressant effect. In the first test, compound **2a** showed an activity comparable to that of minaprine, but with a shorter duration of effect. The same compounds **2a**, **2c** and **2f** significantly and potently antagonized catalepsy induced by prochlorperazine. All the other tested drugs were less active in this test.

The antidepressant potential of the target compounds **2a**—**g** seemed to be partly determined by the number of chlorine atoms on the phenyl nucleus. With regard to structure–activity relationships, introduction of two chlorine atoms at the 2′ and 6′ positions of the phenyl nucleus did not enhance antidepressant activity.

In conclusion, the present study revealed that 3-amino-5-disubstituted benzylidene-6-methyl-4*H*-pyridazines **2** were relatively potent as antidepressant drugs. Compound **2a** showed a dose-dependent antidepressant activity as potent as that of minaprine in the two tests used.

Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. The infrared 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 are designated as follows: s, singlet; br s, broad singlet; m, multiplet.

Chemistry——(2′,6′-Disubstituted benzylidene)-6-methyl-3-(dimethylaminoalkylamino)-4*H*-pyridazine (**2a**—**d**): A solution of a 3-chloropyridazine **1** (0.01 mol) in an excess of a suitable amine (0.1 mol) was refluxed for 24 h. After evaporation *in vacuo* the residue was triturated with diethyl ether and washed with water to provide the expected aminopyridazines. Compounds **2a**—**d** were recrystallized from mixtures of ethanol–water.

(2,6-Disubstituted benzylidene)-6-methyl-3-(2-morpholinoethylamine)-4*H*-pyridazine (**2e**—**g**): A solution of a 3-chloropyridazine **1** (0.01 mol) in an excess of 4-(2-aminoethyl)morpholine (13 g, 0.1 mol) was refluxed for 24 h. After cooling, the solid residue which separated was filtered off and triturated with water until crystallization. Compounds **2e**—**g** were recrystallized from mixtures of ethanol–water.

Pharmacology——All compounds were administered orally in a 0.5% hydroxypropyl methyl cellulose aqueous suspension. Iffa Credo OF1 male mice (20 g) and OFA male Wistar rats (200 g) were used.

Antagonism of Reserpine-Induced Ptosis[4]: This test was performed on groups of 10 mice weighing 20 ± 2 g. Test drugs were administered *p.o.* 1 h before the test. Reserpine was dissolved in a 1% solution of citric acid and administered i.p. at a dose of 2.5 mg/kg: 1, 2 and 4 h later, ptosis was assessed. Animals were hung up by the tail individually for 10 s; when animals did not exhibit ptosis during these 10 s, ptosis was considered as antagonized. Mice were scored individually according to the criteria of Rubin *et al.*[5] Results are expressed as the percentage of protection in comparison with controls.

Antagonism of Prochlorperazine-Induced Catalepsy[6]: Test drugs were administered *p.o.* to groups of 6 rats. One hour later, prochlorperazine was administered i.p. at a dose of 12 mg/kg. Catalepsy was assessed 5 h after the administration of prochlorperazine: each rat was individually placed with its forepaws on a stand 11 cm high and the animals were forced to maintain this abnormal position. A rat which kept the posture for over 20 s was considered as cataleptic. Rats were scored individually according to the following criteria: 2, catalepsy; 1, ambiguous posture; 0, no catalepsy. Results are expressed as the percentage of noncataleptic rats in comparison with the control group.

Data Analysis: Statistical analysis of the results was performed using the method of Schwartz.[7] The data on antagonism of reserpine-induced ptosis were analyzed by using Student's *t*-test. All values of percentage protection in Table III were expressed as mean $\pm$ S.E. Qualitative data on the antagonism of prochlorperazine-induced catalepsy were compared by means of the chisquare test with Yates correction.

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