1-(Substituted benzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidones: A Series with Stimulant and Depressant Activities

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Abstract □ A series of 1-(substituted benzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidones was synthesized primarily by catalytic hydrogenation of the corresponding 1-(substituted benzyl)-2(1*H*)-pyrimidone. The pharmacological evaluation of these compounds in mice revealed a unique profile that included evidence of CNS stimulation and depression within the series and in the same compounds. Some members of this series induced signs of only CNS stimulation, some compounds caused signs of only CNS depression and skeletal muscle relaxation, and some caused signs of both stimulation and depression in the same animal. This apparent dual activity was assessed further in mice with antidepressant tests based on tetrabenazine antagonism and with antianxiety/anticonvulsant tests on the antagonism of a number of convulsants. The 4-chloro-, 4-fluoro-, 4-bromo-, and 3,4-dichlorobenzyl compounds exhibited antidepressant and antianxiety activities in the same dose range. Among these four compounds, the 3,4-dichlorobenzyl compound possessed the lowest antitetrabenazine (17 mg/kg po) and antipentylenetetrazol (23 mg/kg po) ED_{50} values. The 4-fluoro compound antagonized tetrabenazine-, pentylenetetrazol-, and isoniazid-induced tonic convulsions in the same dose range (≃50 mg/kg po).

Keyphrases □ 1-(Substituted benzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidones—synthesis and testing for stimulant and depressant activities, mice □ CNS activity—1-(substituted benzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidones, synthesis and testing for stimulant and depressant activities, mice

Anxiety is a frequent complication of depression (1). Drugs that possess both mood-elevating and anxiolytic properties have been useful in the treatment of this type of disorder (2, 3). The present report describes a series of compounds that exhibited both stimulant and depressant properties (4, 5). Within the same series of 1-(substituted benzyl)-3,4,5,6-tetrahydropyrimidones, some compounds produced signs of central nervous system (CNS) stimulation similar to amphetamine (*i.e.*, signs of excitation followed by depression); other compounds caused only stimulation or depression, and some caused signs of skeletal muscle relaxation.

This report describes the synthesis and pharmacological evaluation of 14 representatives of this class of compounds.

EXPERIMENTAL[1]

Chemistry—*1-(3,4-Dichlorobenzyl)-2(1*H*)-pyrimidone (IIIg)*—A solution of 53.2 g (0.400 mole) of 2-hydroxypyrimidine hydrochloride (I) (6) in 850 ml of methanol was treated with 110 g (0.800 mole) of potassium carbonate, 33.2 g (0.200 mole) of potassium iodide, and 78.2 g (0.400 mole) of α,3,4-trichlorotoluene. The reaction mixture was refluxed for 24 hr and concentrated to dryness *in vacuo*. The residue was slurried with 500 ml of water for 2 hr, and the product was filtered. Recrystallization from acetonitrile gave an analytical sample (Table I); NMR (dimethyl sulfoxide-d_6): δ 5.08 (s, 2H, benzyl CH_2), 6.46 (m, 1H, pyrimidine C-5 H), 7.47 (m, 3H, phenyl CH), and 8.48 (m, 2H, pyrimidine C-4 H and C-6 H); IR: 6.03 (C=O), 6.21, and 6.37 (C=C and C=N) μm.

Pyrimidones III*b* and III*i* were prepared similarly. Compound III*b* was isolated as a hydrochloride, which was prepared by treating a methanolic solution of the product with methanolic hydrogen chloride (Table I).

In the case of III*a*, the reaction mixture was poured into water and the product was collected and suspended in ethanol. Addition of methanolic hydrogen chloride yielded the hydrochloride (Table I).

For III*c*–III*f*, III*h*, III*j*, and III*k*, the reaction mixture was poured into water and the product was extracted with chloroform. The chloroform extract was dried over magnesium sulfate, the solution was concentrated to dryness, and the residue was recrystallized from the appropriate solvent to afford the products (Table I).

The products, III*a*–III*f* and III*h*–III*k*, exhibited IR and NMR spectra consistent with their assigned structures.

*1-(3,4-Dichlorobenzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (X)*—A mixture of 38 g (0.15 mole) of III*g*, 0.60 g of platinic oxide, and 260 ml of methanol was shaken with hydrogen on a Parr apparatus at 3–4 atm for 7 hr. The mixture was warmed, decolorized, and filtered. Concentration to dryness *in vacuo* gave the crude product, which was recrystallized from acetonitrile to give an analytical sample (Table II); NMR (dimethyl sulfoxide-d_6): δ 1.90 (m, 2H, pyrimidine C-5 H), 3.27 (m, 4H, pyrimidine C-4 H and C-6 H), 4.51 (s, 2H, benzyl CH_2), 6.20 (broad s, 1H, pyrimidine N-3 H), and 7.25 (m, 3H, phenyl CH); IR: 3.09, 3.13 (NH), and 6.07 (C=O) μm.

Compounds IV–IX and XI–XIV were prepared similarly (Table II).

*1-(4-Nitrobenzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (XVI)*—A mixture of 20 g (0.20 mole) of 3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (XV), 28 g (0.20 mole) of potassium carbonate, 16.6 g (0.10 mole) of potassium iodide, and 43.2 g (0.200 mole) of α-bromo-*p*-nitrotoluene in 200 ml of dimethylformamide was stirred at 100° for 1.5 hr and poured into 2 liters of iced water. The product was collected and washed with acetone to give XVI (Table II).

The 3-nitro isomer (XVII) was prepared in an analogous manner (Table II).

*1-(4-Acetamidobenzyl) - 3,4,5,6-tetrahydro - 2(1*H*) - pyrimidone (XVIII)*—A slurry of 20.5 g (0.100 mole) of IV and 20.7 g (0.150 ml) of potassium carbonate in 500 ml of benzene was treated with acetyl chloride (12.0 g, 0.150 mole). The mixture was stirred and refluxed for 3 hr and concentrated to dryness *in vacuo*. The residue was slurried with 250 ml of water for 20 min, and the product was filtered, washed with water, and dried to give the crude product. Recrystallization from methanol gave XVIII (Table II).

The IR and NMR spectra of IV–IX, XI–XIV, and XVI–XVIII were consistent with their assigned structures.

Pharmacology—*Gross Observation in Mice*—Groups of three unfasted male mice[2] (TAC:SW/fBr), 20–26 g, were administered oral doses (50–1600 mg/kg) of the test compounds as a 4% suspension in 0.5% methylcellulose 4000 cps[3]. Gross pharmacological effects were rated over a 2-hr period by methods similar to those reported by Irwin (7). Pharmacological effects, including muscle relaxation, behavorial, and autonomic effects, were rated on a scale from 0 to 4, with 0 = no effect, 1 = slight, 2 = moderate, 3 = extreme, and 4 = severe. The animals were returned to their cages; any deaths occurring within 72 hr were recorded, and the highest tolerated dose (the highest dose tested not causing death) was determined.

Tetrabenazine Antagonism—The method used was similar to that described by Barnett *et al.* (8). Groups of five unfasted male mice (TAC:SW/N fBr), 20–27 g, were pretreated with the test compounds at 200 mg/kg po as a 2% suspension in 0.5% methylcellulose or with 0.5% methylcellulose alone. After 30 min, each animal received tetrabenazine methanesulfonate[4] (35 mg/kg ip in saline) or saline in a volume of 10

[1] Melting points were determined on a Mel-Temp apparatus, and those below 230° are corrected. IR spectra were determined as Nujol mulls on a Perkin-Elmer 137B spectrophotometer, and NMR spectra were determined on a Varian A-60A instrument using tetramethylsilane as the internal standard.

[2] Taconic Farms, Germantown, N.Y.

[3] Dow Chemical Co.

[4] Hoffmann–La Roche.

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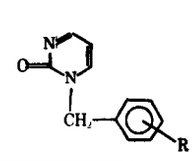


Table I—Physical and Analytical Data for 1-(Substituted benzyl)-2(1*H*)-pyrimidones

Compound	R	Recrystallization Solvent[a]	Melting Point	Yield, %	Formula	Analysis, %	Calc.	Found
IIIa	4-NO_2·HCl	A	199–201°	84	$C_{11}H_9N_3O_3$·HCl	C	49.36	49.22
						H	3.77	3.72
						N	15.70	15.57
IIIb	4-Cl·HCl	B	148–150°	56	$C_{11}H_9N_2O$·HCl	C	51.39	51.80
						H	3.92	3.96
						N	10.81	11.02
IIIc	4-CH_3	C	151–152°	43	$C_{12}H_{12}N_2O$	C	71.98	71.86
						H	6.04	5.83
						N	13.99	14.08
IIId	4-OCH_3	C	129–131°	37	$C_{12}H_{12}N_2O_2$	C	66.65	66.80
						H	5.59	5.62
						N	12.96	13.09
IIIe	4-F	C	158–159°	52	$C_{11}H_9FN_2O$	C	64.70	64.57
						H	4.44	4.33
						N	13.72	13.76
IIIf	4-Br	C	151–159°	68	$C_{11}H_9BrN_2O$	C	49.84	49.74
						H	3.42	3.44
						N	10.57	10.60
IIIg	3,4-Cl	C	184–186°	56	$C_{11}H_8Cl_2N_2O$	C	51.79	51.87
						H	3.16	3.15
						N	10.98	11.15
IIIh	3-F	C	138–140°	49	$C_{11}H_9FN_2O$	C	64.70	64.60
						H	4.44	4.41
						N	13.72	13.77
IIIi	2,4-Cl	C	182–184°	57	$C_{11}H_8Cl_2N_2O$	C	51.79	51.65
						H	3.16	3.17
						N	10.98	11.17
IIIj	2-F	C	110–111°	56	$C_{11}H_9FN_2O$	C	64.70	64.65
						H	4.44	4.34
						N	13.72	13.78
IIIk	3-CF_3	D	89–91°	78	$C_{12}H_9F_3N_2O$	C	56.71	56.51
						H	3.51	3.58
						N	11.02	11.00

[a] Key: A = ethanol, B = isopropanol, C = acetonitrile, and D = toluene.

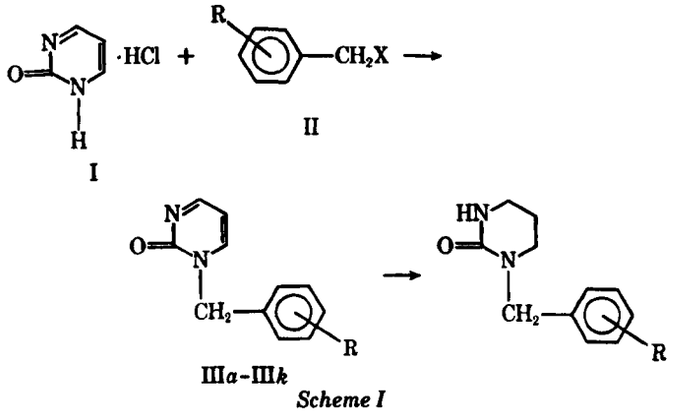
ml/kg. After an additional 30 min, the degree of palpebral narrowing was estimated as a measure of ptosis and compared to methylcellulose and tetrabenazine control groups. The degree of ptosis that developed was evaluated using a rating scale of 0–4, with a score of 4 representing a normal palpebral opening and scores of 3, 2, 1, and 0 representing slight, moderate, marked, and complete active closure of the palpebral opening, respectively. The percent prevention of ptosis was calculated as described by Barnett *et al.* (8).

Compounds that antagonized the effect of tetrabenazine by 50% or greater were evaluated further to establish dose-dependent relationships in mice. The ED_{50} values were calculated using a simple linear regression (9).

Pentylenetetrazol Antagonism—The method used was a modification of that described by Goodman *et al.* (10). Groups of five unfasted male mice (TAC:SW/N fBr), 19–27 g, were pretreated with the test compounds at a dose of 200 mg/kg po as a 2% suspension in 0.5% methylcellulose or with 0.5% methylcellulose alone at 10 ml/kg. One hour later, each animal received pentylenetetrazol[5] (45 mg/kg iv as a 0.45% solution in saline). Seizures usually occurred within 1 min, and mice that failed to exhibit tonic extensor seizures within 2 min were recorded as protected. The results were expressed as the percent protected in any treatment group.

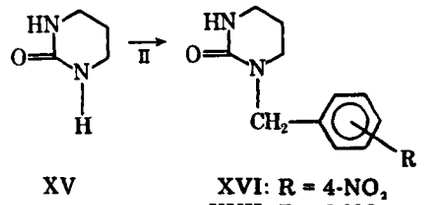
Compounds that were effective at a dose of 200 mg/kg po in preventing the seizure in at least 60% of the mice then were tested for dose-dependent effects. The ED_{50} values were calculated using a simple linear regression (9).

Other CNS Stimulation Antagonism—The method used was a modification of that described by Costa *et al.* (11). Groups of 10 male mice (TAC:SW/N fBr), 19–27 g, were pretreated with the test compound at a dose of 200 mg/kg po as a 2% suspension in 0.5% methylcellulose or with 0.5% methylcellulose alone at 10 ml/kg. After 30 min, each animal received one of the following agonists, administered intraperitoneally: strychnine sulfate[6], 2 mg/kg as a 0.02% solution in saline; pentylenetetrazol, 112.5 mg/kg as a 1.125% solution in saline; isoniazid[7], 340 mg/kg as a 3.4% so-



IIIa–IIIk

Scheme I



XV XVI: R = 4-NO_2 XVII: R = 3-NO_2

Scheme II

[5] Knoll.
[6] Humco Laboratories.
[7] City Chemical Corp.

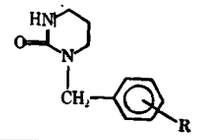


Table II—Physical and Analytical Data for 1-(Substituted benzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidones

Compound	R	Precursor	Recrystallization Solvent[a]	Melting Point	Yield, %	Formula	Analysis, %	Calc.	Found
IV	4-NH_2	III*a*	A	161–163°	79	$C_{11}H_{15}N_3O$	C	64.37	64.38
							H	7.37	7.25
							N	20.47	20.32
V	4-Cl	III*b*	A	131–133°	62	$C_{11}H_{13}ClN_2O$	C	58.80	59.09
							H	5.83	6.00
							N	12.47	12.45
VI	4-CH_3	III*c*	A	126–128°	73	$C_{12}H_{16}N_2O$	C	70.56	70.63
							H	7.90	7.89
							N	13.72	13.78
VII	4-OCH_3	III*d*	A	107–108°	66	$C_{12}H_{16}N_2O_2$	C	65.43	65.46
							H	7.32	7.36
							N	12.72	12.69
VIII	4-F	III*e*	A	140–142°	52	$C_{11}H_{13}FN_2O$	C	63.45	63.50
							H	6.29	6.12
							N	13.46	13.52
IX	4-Br	III*f*	B	134–136°	43	$C_{11}H_{13}BrN_2O$	C	49.09	49.04
							H	4.87	4.85
							N	10.41	10.33
X	3,4-Cl	III*g*	A	120–122°	77	$C_{11}H_{12}Cl_2N_2O$	C	50.98	51.15
							H	4.67	4.71
							N	10.81	10.90
XI	3-F	III*h*	A	147–149°	83	$C_{11}H_{13}FN_2O$	C	63.45	63.67
							H	6.29	6.25
							N	13.46	13.62
XII	2,4-Cl	III*i*	A	152–156°	83	$C_{11}H_{12}Cl_2N_2O$	C	50.98	50.99
							H	4.67	4.67
							N	10.81	10.98
XIII	2-F	III*j*	A	131–134°	84	$C_{11}H_{13}FN_2O$	C	63.45	63.45
							H	6.29	6.23
							N	13.46	13.45
XIV	3-CF_3	III*k*	A	97–99°	66	$C_{12}H_{13}F_3N_2O$	C	55.81	55.86
							H	5.07	5.07
							N	10.85	10.91
XVI	4-NO_2	XV	C	189–191°	47	$C_{11}H_{13}N_3O_3$	C	56.16	56.31
							H	5.57	5.58
							N	17.86	18.05
XVII	3-NO_2	XV	C	144–146°	20	$C_{11}H_{13}N_3O_3$	C	56.16	55.99
							H	5.57	5.63
							N	17.86	17.52
XVIII	4-$NHCOCH_3$	IV	D	219–226°	48	$C_{13}H_{17}N_3O_2$	C	63.14	62.88
							H	6.93	7.00
							N	16.99	16.96

[a] Key: A = acetonitrile, B = acetone, C = water, and D = methanol.

lution in saline; picrotoxin[8], 15 mg/kg as a 0.15% solution in saline; and harmaline[8], 50 mg/kg as a 0.5% solution in saline.

Strychnine-, pentylenetetrazol-, and picrotoxin-induced seizures usually occurred within 5–15 min, and mice that failed to exhibit these seizures within 30 min were considered protected. Isoniazid-induced seizures usually occurred within 30–50 min, and mice that failed to exhibit these seizures within 90 min were considered protected. Harmaline caused a sustained tremor of the head and limbs usually within 15 min, and mice that failed to exhibit this tremor within 30 min were considered protected. The results were expressed as the percent protected in each treatment group.

Compounds effective at a dose of 200 mg/kg po in preventing the seizures or tremors in at least 60% of the mice then were tested for dose-dependent effects. The ED_{50} values were calculated using a simple linear regression (9).

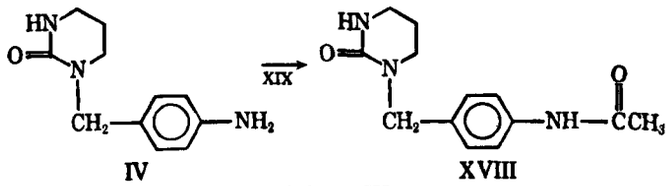
RESULTS

Chemistry—Most of the target compounds were prepared in a two-step sequence originating with 2-hydroxypyrimidine hydrochloride (I). Alkylation of I with the appropriate benzyl halide (II) afforded the pyrimidones (III*a*–III*k*), which in some cases were characterized as their hydrochlorides (Table I). Use of potassium iodide in the sequence improved the product yields. Carbonyl absorption in the IR spectra of the products showed that alkylation occurred on nitrogen rather than oxygen. Catalytic hydrogenation of the free bases in the presence of platinic oxide gave the desired reduced compounds. The amino compound (IV) was prepared by hydrogenation of the nitro compound (III*a*), while the substituents in pyrimidones III*b*–III*k* remained unchanged in their conversion to V–XIV (Table II) (Scheme I).

Since the final step in this sequence involves hydrogenation, it is unsuitable for the preparation of tetrahydropyrimidines containing the nitrobenzyl function. This type of compound was synthesized by direct alkylation of 3,4,5,6-tetrahydro-2-pyrimidone (XV) with the appropriate nitrobenzyl halide (II) (Scheme II). Poor yields in these reactions rendered the original sequence originating with I as the method of choice for the preparation of pyrimidones containing functions that are not susceptible to hydrogenation.

The acetamido compound (XVIII) was prepared by reaction of IV with acetyl chloride (XIX) (Scheme III).

Pharmacology—Four compounds (V and VIII–X) antagonized the actions of tetrabenazine and pentylenetetrazol in the same dose range.



Scheme III

[8] Aldrich Chemical Corp.

Table III—Pharmacological Evaluation of Tetrahydropyrimidones and Selected Reference Drugs

Compound	R	Gross Effect[a]	HTD[b] (LD_{50}), mg/kg po	Anti-TBZ[c] ED_{50}	Anti-PTZ[d] ED_{50}	Anti-Iso[e] ED_{50}	Anti-Picro[f] ED_{50}	Anti-PTZ[g] ED_{50}	Anti-Strych[h] ED_{50}	Anti-Harm[i] ED_{50}
IV	4-NH_2	Stimulation and muscle relaxation	800	27	187	136	>200	>200	>200	>200
V	4-Cl	Depression	400	51	84	41	>200	>200	>200	>200
VI	4-CH_3	Stimulation, depression, and muscle relaxation	800	134	>200	69	>200	>200	>200	>200
VII	4-OCH_3	Stimulation	1600	20	>200	>200	>200	>200	>200	>200
VIII	4-F	Stimulation, muscle relaxation, and depression	800	43	56	52	>200	>200	>200	>200
IX	4-Br	Stimulation and depression	400	150	145	72	>200	>200	>200	>200
X	3,4-Cl	Stimulation, depression, and muscle relaxation	400	17	23	146	>200	>200	>200	>200
XI	3-F	Muscle relaxation and depression	400	108	180	109	>200	>200	>200	>200
XII	2,4-Cl	Depression and muscle relaxation	800	>200	45	45	186	>200	>200	>200
XIII	2-F	Depression and muscle relaxation	800	>200	57	76	>200	>200	>200	>200
XIV	3-CF_3	Muscle relaxation and depression	800	>200	37	—	>200	>200	>200	>200
XVI	4-NO_2	Muscle relaxation and depression	800	97	>200	>200	>200	>200	>200	>200
XVII	3-NO_2	Depression	400	174	>200	>200	>200	>200	>200	>200
XVIII	4-$NHCOCH_3$	Stimulation and depression	1600	134	>200	>200	>200	>200	>200	>200
Reference compounds										
Amitriptyline	—		(320)	1.1	37	26	>50	>50	>50	>50
Chlordiazepoxide	—		(832)	>100	4.3	22	23	9	>100	>100
d-Amphetamine	—		(9)	6.5	>10	>10	>10	>10	>10	>10
Desipramine	—		(804)	0.3	>100	>100	>100	>100	>100	>100
Diazepam	—		(772)	>100	0.4	0.6	19	2.7	>100	35
Doxepin	—		(275)	5.4	78	—	—	—	—	—
Glutethimide	—		(595)	100	23	36	>100	33	>100	>100
Imipramine	—		(342)	1.3	50.2	<100	>100	>100	>100	>100

[a] Signs are listed in order of appearance. [b] HTD = highest tolerated dose; LD_{50} = dose of drug causing lethality in 50% of the animals. [c] Anti-TBZ = dose of drug causing 50% antagonism of tetrabenazine-induced ptosis. [d] Anti-PTZ = dose of drug causing 50% antagonism of pentylenetetrazol-induced tonic extensor seizure. [e] Anti-Iso = dose of drug causing 50% antagonism of isoniazid-induced tonic extensor seizure. [f] Anti-Picro = dose of drug causing 50% antagonism of picrotoxin-induced tonic extensor seizure. [g] Anti-PTZ = dose of drug causing 50% antagonism of pentylenetetrazol-induced clonic seizures. [h] Anti-Strych = dose of drug causing 50% antagonism of strychnine-induced tonic seizures. [i] Anti-Harm = dose of drug causing 50% antagonism of harmaline-induced tremors.

Compound X exhibited the lowest ED_{50} values for antitetrabenazine and antipentylenetetrazol activity (17 and 23 mg/kg, respectively); VIII yielded ED_{50} values of 43 and 56 mg/kg, respectively. Compound VIII also possessed anti-isoniazid activity with an ED_{50} value of 52 mg/kg. Indeed, the anti-isoniazid test appears to be the most specific test for antianxiety activity (11).

The combination of antidepressant and antianxiety activities is a unique pharmacological property of these compounds. Furthermore, the fact that these activities are present in the same dose range distinguishes these compounds from known antidepressant/antianxiety compounds such as doxepin and amitriptyline (Table III). For example, doxepin was more than 10 times less active in the antipentylenetetrazol test compared to the antitetrabenazine test.

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Pharmacology of 1-(3,4-Dichlorobenzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone, a Novel Antidepressant Compound with Antianxiety Activity

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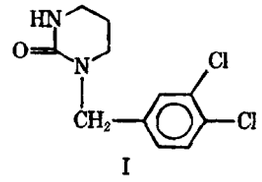
Abstract □ 1-(3,4-Dichlorobenzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (I) was evaluated in selected pharmacological tests, and its activity was compared to that of some clinically useful psychotropic drugs. Based on the results, it is evident that I has a unique profile of antidepressant and antianxiety activities that are evident in the same dose range. The mechanism of its antidepressant activity is proposed to be similar to the tricyclic antidepressants, that is, inhibition of norepinephrine uptake. Neither I nor the tricyclic antidepressants possess monoamine oxidase-inhibiting activity. However, unlike the tricyclic antidepressants, I is devoid of any significant anticholinergic activity and presumably is free of anticholinergic side effects.

Keyphrases □ 1-(3,4-Dichlorobenzyl) - 3,4,5,6-tetrahydro-2(1*H*)-pyrimidone—evaluation of antidepressant and antianxiety activity, *in vitro* and *in vivo* □ CNS activity—1-(3,4-dichlorobenzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone, evaluation of antidepressant and antianxiety activity, *in vitro* and *in vivo*

The synthesis of a series of 1-(substituted benzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidones (1) and the identification of the unique antidepressant/antianxiety properties of several of these compounds were reported previously (2). Three compounds in this series antagonized tetrabenzine- and pentylenetetrazol-induced effects within the same dose range. The 3,4-dichlorobenzyl derivative (I) was the most potent compound and had the least separation between the antidepressant and anxiolytic doses (antitetrabenazine ED_{50} value of 23 mg/kg po and antipentylenetetrazol ED_{50} value of 18 mg/kg).



I

This report discusses the pharmacology of 1-(3,4-dichlorobenzyl)-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone[1], a compound with antidepressant/antianxiety properties.

EXPERIMENTAL

Drugs—The experimental drugs used were acetylcholine chloride[2], amitriptyline hydrochloride[3], *d*-amphetamine sulfate[4], apomorphine hydrochloride[5], atropine sulfate[6], deprenyl[7], desipramine hydrochloride[8], doxepin hydrochloride[9], *l*-epinephrine bitartrate[10], histamine phosphate[11], imipramine hydrochloride[12], methylphenidate hydrochloride[13], *l*-norepinephrine (levarterenol) bitartrate[10], nortriptyline hydrochloride[14], pargyline hydrochloride[15], pentylenetetrazol[16], protriptyline hydrochloride[3], serotonin creatinine sulfate[17], tetrabenazine methanesulfonate[18], tripelennamine hydrochloride[19], and tyramine hydrochloride[20].

[1] EU-2841, Norwich-Eaton Pharmaceuticals, Division of Morton-Norwich Products.
[2] Merck & Co.
[3] Merck Sharp & Dohme.
[4] Smith Kline and French.
[5] Mallinckrodt.
[6] Amend.
[7] Chinoin Budapest.
[8] USV.
[9] Pfizer.
[10] Winthrop.
[11] Burroughs Wellcome.
[12] Geigy.
[13] Ciba.
[14] Lilly.
[15] Abbott.
[16] Knoll.
[17] Nutritional Biochemical Corp.
[18] Hoffmann–La Roche.
[19] Ciba-Geigy.
[20] Aldrich Chemical Co.

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