United States Patent Office 3,755,584 Patented Aug. 28, 1973

3,755,584

TRANQUILIZERS

Nicholas Peter Plotnikoff, Lake Bluff, Ill., assignor to Abbott Laboratories, North Chicago, Ill.

No Drawing. Filed Apr. 3, 1972, Ser. No. 240,770
Int. Cl. A61k 27/00
U.S. Cl. 424—263 4 Claims

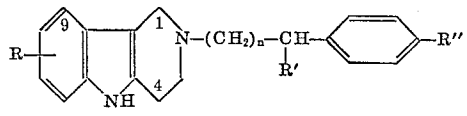
ABSTRACT OF THE DISCLOSURE

γ-Carbolines carrying fluorine in the 6- or 8-position and a specific p-substituted phenylalkyl moiety at the 2-position were found to be major tranquilizers at low doses in warm-blooded animals.

DETAILED DESCRIPTION OF THE INVENTION

Many of the known antipsychotics (major tranquilizers) are very active in reducing hyperactivity and stereotypy induced by methamphetamine but, unfortunately, that desirable activity is often accompanied by sedative effects and tremors (Psychopharmacology; A Review of Progress 1957–1967, Public Health Service, Publication No. 1836 of 1968, Session XI). A new series of compounds has now been found which in its desirable antipsychotic potency is similar to chlorpromazine but produces no or almost no parkinson-like side effects or sedation.

The new series is represented by the formula



wherein R is fluorine at the 6- or 8-position, R′ is hydrogen or hydroxy, R″ is fluorine, amino or acetylamino and *n* is 1 or 3. When these compounds are administered orally at doses of 0.5–20 mg./kg. to warm-blooded animals, strong tranquilization is achieved with no parkinson-like side effects and with minor sedative effects only in the upper range of the given dose limit. Acute toxicity studies in mice, rats, dogs and monkeys indicate a wide margin of safety or, expressed differently, the compounds of Formula I have a very high therapeutic index.

In order to show the efficacy of the new compounds, standard test methods were used in animals and comparative tests were carried out with commercial tranquilizers.

Example 1

The antogonism of methamphetamine-induced hyperactivity in mice was evaluated in motor activity chambers equipped with photocells connected to a counting device. Groups of mice were subcutaneously injected with 3 mg./kg. of methamphetamine 2 hours after they had received an oral dose of the compound of Formula I wherein R is fluorine in the 8-position, R′ is hydrogen, R″ is fluorine and $n=3$. Three mice were placed in each chamber and a total of 9 mice were used per test dose. Changes in motor activity recorded are shown in the Table I.

TABLE I

Oral dose	2-hour mean count ± S.E.	Change over control, percent	Change with chlorpromazine, percent
Methamphetamine	13,837±1,037	(1)	(1)
Methamphetamine + 5 mg./kg. test drug	6,384±774	−54	−30
Methamphetamine + 10 mg./kg. test drug	5,034±1,588	−64	−83
Methamphetamine + 20 mg./kg. test drug	2,397±903	−83	−92

[1] Control.

In the above table, the last column represents the difference in activity chamber counts over the methamphetamine control when chlorpromazine is administered as the test drug in the same dose as listed for the test drug. The table clearly points out that for reducing hyperactivity, the above test drug, 8-fluoro-2-(4-x-fluorophenylbutyl)-1,2,3,4-tetrahydro-γ-carboline, is comparable with chlorpromazine, although at the lower dose range, the new compound appears to be more efficient. No sedative action was noted with the test animals upon gross observation during and following the above 2 hour test.

Using the same procedure and setting but without inducing hyperactivity with methamphetamine, the above test in mice shows a motor-activity reduction of 18% at 5 mg./kg., 60% at 10 mg./kg. and 66% at 20 mg./kg. Overt sedative effects (atoxia) were seen only at very high doses (1000 mg./kg.).

Example 2

By following the same procedure as shown in Example 1 but using rats weighing between 200 and 300 g. as the test animals, the above identified compound showed the activity reduction listed in Table II.

TABLE II

Oral dose	2-hour mean count±S.E.	Change over control, percent	Test drug alone, percent
Methamphetamine	8,206±1,262	(1)	
Methamphetamine + 5 mg./kg. test drug	4,762±127	−42	−54
Methamphetamine + 10 mg./kg. test drug	2,243±401	−73	−82
Methamphetamine + 20 mg./kg. test drug	1,720±626	−79	−90

[1] Control.

Table II shows similarly to Table I that the test compound identified above significantly reduces hyperactivity induced by methamphetamine.

Example 3

8 - fluoro-2-(4-p-fluorophenylbutyl)-1,2,3,4-tetrahydro-γ-carboline was administered orally to dogs at doses of 0.25–20 mg./kg. followed in 2 hours with an oral dose of 5 mg./kg. of methamphetamine. The motor activity of the test dogs was measured on an activity scale of 0–3 with 3 being used for pronounced effects. In control animals, doses of 5 mg./kg. of methamphetamine produced ratings of 3 in activity increase, mydriasis and sterotypy. When the methamphetamine was followed by 0.25 and 0.5 mg./kg. of the test drug, one of two dogs of each dose level showed a 2 rating in stereotypy while all other symptoms for all 4 animals involved were the same as in the control animals. At a dose of 1 mg./kg. mydriasis was reduced to 2 in one dog, sterotypy was reduced to 2 in two animals and to 1 in the other two dogs. The higher doses produced the results shown in Table III.

TABLE III

Dose level, mg./kg.	Increased activity	Mydriasis	Stereotypy
2	0	3	1
	3	3	1
4	1	1	1
	2	1	0
5	2(2)	2(2)	1(2)
	2(2)	2(2)	0(1)
10	1(3)	2(2)	0(3)
	1(1)	0(1)	0(0)
20[1]	[1] 1	[1] <0.5	[1] 0

[1] Average of 6 dogs.

The values shown in parentheses above are those observed when the test drug is chlorpromazine. The above results, alone or in comparison with the commercial material, clearly show the pronounced effect of the tested drug.

Three other dogs were treated with the same drug at an oral dose of 10 mg./kg./day for 5 days. No behavorial or neurological effects were seen. At higher doses (20 mg./kg.) this subacute test showed tremors on the 3rd and 5th day. When this test was carried out with chlorpromazine, tremors and decreased activity were observed already at lower doses.

Example 4

The same compound as used in the preceding examples was tested orally in monkeys made hyperactive with methamphetamine doses of 5 mg./kg. At an oral treatment dose of 1–5 mg./kg. a significant reduction of stereotypy (head weaving and bobbing) and hyperactivity was observed. At higher doses (10–20 mg./kg.) stereotypy and hyperactivity were not only antagonized but spontaneous motor activity was also reduced significantly. Similar antagonism was observed with chlorpromazine at doses of 2.5–5 mg./kg.

Chronic toxicity studies revealed that tremors were seen only at doses of 20–40 mg./kg. establishing a wide margin of safety. Oral doses of 100–1000 mg./kg. administered as a 5–25% tragacanth suspension produced moderate to marked sedative effects lasting up to 4 days. All 14 animals used in this test recovered fully by the fifth day.

Example 5

The methamphetamine test described above was carried out for other compounds encompassed by structure I. In this test, a group of mice were intraperitoneally treated with the test compound and the activity decrease measured in percent reduction from a control group. In all instances, the animals received 3 mg./kg. of methamphethamine by the subcutaneous route and 2 hour activity comparisons were recorded in Table IV. Also shown in Table IV are the values observed in the modified DOPA test described by Everett in Proc. 1st Intl. Symp. Anti-depressant Drugs (Excerpta Med. Int. Congr. Sec. No. 122 of 1966) using a scale of 0–3.

TABLE IV

No.	Compound of structure I R(position)	R′	R″	n	Dose, mg./kg.	Decrease in activity, percent	Antidepressant effect 25 mg./kg.	100 mg./kg.
1	F(8)	H	F	3	20	91	1	1
2	F (8)	OH	F	3	50	95	1	1
3	F (8)	H	NH_2	1	50	93	2	3
4	F (8)	H	NHAc	1	50	93	2	2
5	F (8)	H	NH_2	3	50	92	2	2
6	F (6)	H	F	3	50	79	2	2

As demonstrated above, warm-blooded animals exhibit strong tranquilization when treated with a compound of structure I in doses similar or below amounts of commercial tranquilizers. In addition, the new treatment shows significant advantages over other drugs used for this type of therapy: tremors and sedation are totally absent when a dose within the lower effective amount is administered. The oral dosage range is therefore preferably chosen within the range of 1–5 mg./kg. In many instances, the therapeutic index is as high as 1000 since the oral LD_{50} values of the above compounds are mostly between 250 and above 1000 mg./kg.

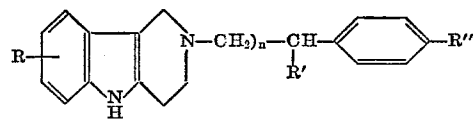
The term tranquilizing as used in this disclosure is meant to indicate primarily the reduction of hyperactivity and stereotypy as induced in test animals by methamphethamine. For higher animals and humans, the test results shown clearly indicate the advantageous use of the new compounds in treatment of schizophrenia, psychosis and depressions, whether these symptoms are clinical or brought on by hallucinogens.

While the above examples show, for the main part, the oral route of administration, intramuscular, intravenous and other routes are similarly useful. For intravenous administration, a dosage range of 0.1–5 mg./kg. is preferred while the intramuscular dose range is similar to the oral dose. For parenteral administration, the above drugs are preferably dissolved in physiological saline while oral dosage forms may be prepared in tablet, capsule, wafer or pill form according to well-known principles. For all routes, the above compounds may be processed and administered in their base form or suitable pharmacologically acceptable salts may first be prepared. Particularly suitable are the acid addition salts formed with hydrochloric, sulfuric, phosphoric, acetic, succinic, tartaric or citric acid. Injectable solutions are preferably adjusted to a pH of 7 or slightly above by the use of a suitable buffer.

The compounds used in the present invention are prepared by the method set forth in U.S. Pat. 3,654,289.

I claim:

1. The process of tranquilizing a warm-blooded animal comprising administering to said animal a small but tranquilizing amount of a compound of the formula



wherein R is fluorine attached to the 6- or 8-position, R′ is hydrogen or hydroxy, R″ is fluorine, amino or acetylamino and *n* is 1 or 3 or a non-toxic acid addition salt thereof.

2. The process of claim 1 wherein said compound or a non-toxic salt thereof is administered orally at a dose of between 0.5 and 20 mg./kg.

3. The process of claim 2 wherein said amount is between 1 and 5 mg./kg.

4. The process of claim 2 wherein said compound is 8-fluoro-2-(3-p-fluorophenylbutyl)-1,2,3,4 - tetrahydro-γ-carboline.

References Cited

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STANLEY J. FRIEDMAN, Primary Examiner

UNITED STATES PATENT OFFICE

Certificate

Patent No. 3,755,584 Patented August 28, 1973

Nicholas Peter Plotnikoff

Application having been made by Nicholas Peter Plotnikoff, the inventor named in the patent above identified, and Abbott Laboratories, North Chicago, Illinois, a corporation of Illinois, the assignee, for the issuance of a certificate under the provisions of Title 35, Section 256, of the United States Code, adding the name of Robert P. Johnson as a joint inventor, and a showing and proof of facts satisfying the requirements of the said section having been submitted, it is this 2nd day of July 1974, certified that the name of the said Robert P. Johnson is hereby added to the said patent as a joint inventor with the said Nicholas Peter Plotnikoff.

FRED W. SHERLING,
Associate Solicitor.