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Molloy

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[54] **PHARMACEUTICAL COMPOSITIONS CONTAINING SUBSTITUTED 2-OXO-INDOLINES AND THE USE THEREOF TO TREAT ANXIETY AND TENSION**

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[52] **U.S. Cl.** **424/274**

[51] **Int. Cl.** **A61u 27/00**

[58] **Field of Search** ..... 424/274; 260/325 R

[56] **References Cited**

UNITED STATES PATENTS

3,634,453	1/1972	McManus et al.	260/325 R
3,691,199	9/1972	Kobaysahi et al.	260/325 R
3,720,771	3/1973	Canas-Rodriguez et al.	424/274
3,723,457	3/1973	Hirose et al.	424/274

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[57] **ABSTRACT**

A pharmaceutical composition containing as an active ingredient a 2-oxo-indoline substituted on the benzene ring by C_1–C_3 alkyl, C_1–C_3 alkoxy, halo, or trifluoromethyl, and a method of using the substituted 2-oxoindoline in relieving a condition associated with anxiety, tension, or a like emotional disturbance.

16 Claims, No Drawings

PHARMACEUTICAL COMPOSITIONS CONTAINING SUBSTITUTED 2-OXO-INDOLINES AND THE USE THEREOF TO TREAT ANXIETY AND TENSION

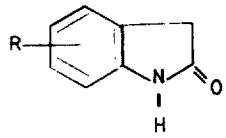
BACKGROUND AND SUMMARY OF THE INVENTION

This invention relates to therapeutic compositions, and to a process for achieving therapeutic action.

It has been discovered that certain substituted 2-oxo-indolines have a useful effect on the central nervous system. In particular, it has been discovered that these compounds exhibit a sedative-hypnotic effect and can be used in the treatment of conditions associated with anxiety, tension, or other emotional disturbance.

2-Oxo-indolines are widely recognized in the art; see, for example, British Pat. No. 1,247,113 and Belgian Pat. No. 756,447. Nowhere, however, does the art recognize that ring-substituted 2-oxo-indolines having the structure defined herein exhibit a useful therapeutic activity. This discovery forms the basis of this invention.

Specifically, this invention relates to a pharmaceutical composition for relieving a condition associated with anxiety, tension, or like emotional disturbance comprising a therapeutically effective dose of an oxo-indoline of the formula

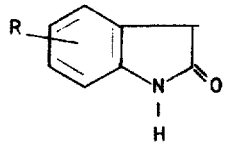


in which R is C_1–C_3 alkyl, C_1–C_3 alkoxy, halo, or trifluoromethyl, in association with a pharmaceutical carrier.

Another embodiment of this invention relates to a method of treating a patient to relieve a condition associated with anxiety, tension, or like emotional disturbance which comprises administering to said patient an oxo-indoline of the foregoing formula.

DETAILED DESCRIPTION OF THE INVENTION

The active compounds of the composition of this invention and useful in the process of this invention have the formula



in which R has the aforementioned definition.

As used in the definition of R, the term "halo" refers to any of fluoro, chloro, bromo, and iodo.

Illustrative of the compounds are the following:

2-Oxo-4-methylindoline;
2-Oxo-6-methylindoline;
2-Oxo-5-ethylindoline;
2-Oxo-7-ethylindoline;
2-Oxo-4-(1-propyl)indoline;
2-Oxo-5-(1-propyl)indoline;
2-Oxo-7-(2-propyl)indoline;
2-Oxo-6-(2-propyl)indoline;
2-Oxo-4-methoxyindoline;
2-Oxo-7-ethoxyindoline;
2-Oxo-5-(1-propoxy)indoline;
2-Oxo-6-(2-propoxy)indoline;

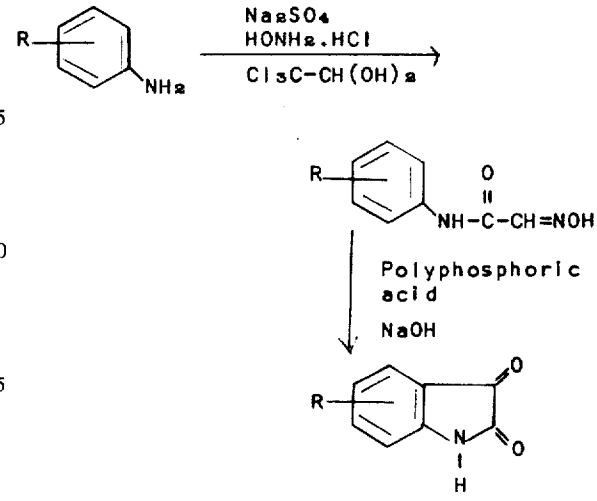
2-Oxo-4-iodoindoline;
2-Oxo-6-bromoindoline;
2-Oxo-5-fluoroindoline;
2-Oxo-6-iodoindoline;
2-Oxo-4-trifluoromethylindoline;
2-Oxo-5-trifluoromethylindoline;
and the like.

Oxo-indolines such as the above can be prepared by any of several recognized methods.

One standard chemical procedure which is available is that commonly referred to as the Stolle synthesis. This is developed at some depth in P. L. Julian et al., *Heterocyclic Compounds*, Vol. 3, John Wiley and Sons, Inc., New York (1952), pp. 142–146, and involves ring-closure of an α-haloacetanilide to the corresponding oxo-indoline. In applying this method to the preparation of compounds defined herein, the particular α-haloacetanilide which is employed will be ring-substituted so as to reflect the position and identity of the ring substituent of the final product.

Another method which is available comprises reduction of the corresponding isatin to the oxo-indoline. This procedure also is described in the aforementioned publication by P. L. Julian et al., at pp. 129–130, thereof.

The isatins which are reduced to the corresponding oxo-indolines can be prepared from readily available starting materials in accordance with the following sequence:



The foregoing sequence is merely representative of the preparation of isatins. Isatins are well known in the art and are available from various routes, see, for example, D. J. Bauer and P. W. Sadler, *Brit. J. Pharmacol.*, 15, (1960) pp. 101–110.

In the foregoing sequence, the source of the isatin is a substituted aniline. Typically, the substituted aniline, in the form of its acid addition salt, is converted to the corresponding isonitrosoacetanilide by reaction with chloral hydrate in the presence of sodium sulfate followed by treatment of the resulting reaction mixture with hydroxylamine hydrochloride. The reaction typically is carried out in water with the reaction mixture being gently heated for a short period of time.

The next step in the synthesis involves the conversion of the isonitrosoacetanilide to its corresponding isatin. This ring-closure reaction can be accomplished by treating the isonitrosoacetanilide with polyphosphoric

acid at a moderately elevated temperature. Since ring-closure occurs in the position ortho to the anilide nitrogen, two structures can be formed, depending upon the position of the substituent on the ring of the isonitrosoacetanilide and the direction of the ring-closure. In the event two products are formed, separation typically can be accomplished by a successive precipitation technique. The reaction product mixture is first brought into aqueous solution by addition of alkali. Precipitation of the two products typically is pH dependent, and one product is precipitated from the solution by acidifying the mixture to a moderately acidic pH of from about 3 to about 5. This product is then collected by filtration or extraction, and the collected product is further purified by standard techniques such as recrystallization. The filtrate then is further acidified, for example, to about pH 1 to effect isolation of the other product. This product is then separately collected and purified by recrystallization from an appropriate solvent.

The final step in the synthesis from isatins of the oxo-indolines used in this invention involves the conversion of the isatin to its corresponding ring-substituted 2-oxo-indoline. This can be accomplished by treating the isatin with anhydrous hydrazine at reflux in an appropriate moderately low boiling solvent such as a lower alkyl alcohol. The resulting unisolated isatin derivative, in the form of a hydrazone, is then reacted reductively with a sodium alkoxide. The overall effect is the replacement of the keto function in the 3-position with a methylene group, thereby achieving formation of the oxo-indoline. Recovery can be accomplished by evaporating the solvent, dissolving the residue in water to achieve solution of the water-soluble by-products, and acidification of the mixture to produce precipitation of the final product. The final product can then be purified by recrystallization from a suitable solvent.

In accordance with this invention, the pharmaceutically active oxo-indolines can be administered alone or, preferably, in association with a pharmaceutical carrier. The pharmaceutical carrier is selected on the basis of the chosen route of administration and in accordance with standard pharmaceutical practice. For example, the oxo-indolines can be administered orally, either alone, in capsule form, or in the form of tablets or capsules containing excipients such as starch, milk sugar, certain types of clay, and the like. The oxo-indolines can also be administered orally in the form of elixirs or oral suspensions which can contain coloring and/or flavoring agents. The oxo-indolines can also be administered parenterally, and, for use in this route of administration, they can be prepared in the form of sterile solutions containing other solutes such as salt or glucose in sufficient quantity to make the solution isotonic. For intramuscular administration, the oxo-indoline compositions can be prepared in an oil base such as a peanut or sesame oil.

The oxo-indolines of this invention are administered in pharmaceutically effective amounts. Generally, these will range from about 0.5 to about 500 milligrams per day, and preferably from about 2 to about 200 milligrams per day. However, in general, the dosage will depend upon particular circumstances, and these may differ from case to case. For example, the dosage levels will vary with the age, weight, and general health of the recipient as well as various other factors which may be peculiar to the particular recipient. In general, if the oxo-indoline is administered by a parenteral route, a lower dosage, for example, from about 0.1 milligram to about 250 milligrams of the oxo-indoline can be employed. Preferably the oxo-indoline composition is in unit dosage form. This expression as used herein refers to a physically discrete unit containing a predetermined dose of the oxo-indoline either alone or in association with a pharmaceutically acceptable carrier or excipient. The unit dosage form may contain from about 0.5 to about 500 milligrams of the active oxo-indoline ingredient.

The following examples are provided to further illustrate the teaching of this invention and are by no means intended to be limiting upon the scope thereof.

EXAMPLE

To a suspension of 15 g. of 6-chloroisatin in 180 ml. of ethanol were added 30 ml. of hydrazine (97%), and the resulting solution was refluxed for 6 hours. A sodium ethoxide solution was prepared by dissolving 8.3 g. of sodium in 350 ml. of ethanol. The reaction mixture from the reaction of 6-chloroisatin and hydrazine, while hot, was slowly added to the sodium ethoxide solution maintained at 60°–70°C. Upon completion of the addition, the resulting mixture was refluxed for about 16 hours. The solvent was then removed in vacuo, and the residue was added to about 800 g. of ice water. The pH of the resulting mixture was adjusted to about pH 1–2 by addition of concentrated hydrochloric acid, and the solids which formed were removed by filtration and washed with water. Recrystallization from a mixture of ethanol and water afforded 7.5 g. of 2-oxo-6-chloroindoline, m.p. 189°–192°C.

Analysis, calculated for C_8H_6ClNO
C, 57.33; H, 3.61; N, 8.36; O, 9.55; Cl, 21.15.
Found: C, 57.37; H, 3.80; N, 8.31; O, 9.29; Cl, 20.85.

Using procedures similar to the above, the following compounds are prepared.

2-Oxo-6-methylindoline; m.p. 171°–173°C.
Anal. Calcd for C_9H_9NO:
C, 73.45; H, 6.16; N, 9.52; O, 10.87.
Found: C, 73.18; H, 6.12; N, 9.80; O, 10.97.

2-Oxo-6-methoxyindoline; m.p. 152°–155°C.
Anal. Calcd for $C_9H_9NO_2$:
C, 66.24; H, 5.56; N, 8.58; O, 19.61.
Found: C, 65.97; H, 5.39; N, 8.85; O, 19.75.

2-Oxo-4-methylindoline; m.p. 204°–206°C.
Anal. Calcd for C_9H_9NO:
C, 73.45; H, 6.16; N, 9.52; O, 10.87.
Found: C, 73.29; H, 6.36; N, 9.58; O, 10.80.

2-Oxo-5-chloroindoline; m.p. 197°–199°C.

2-Oxo-4-chloroindoline; m.p. 211°–213°C.
Anal. Calcd for C_8H_6ClNO:
C, 57.33; H, 3.61; N, 8.38; O, 9.55; Cl, 21.15.
Found: C, 57.54; H, 3.88; N, 8.32; O, 9.69; Cl, 21.21.

2-Oxo-6-fluoroindoline; m.p. 139°–141°C.
Anal. Calcd for C_8H_6FNO:
C, 65.58; H, 4.00; N, 9.23.
Found: C, 65.76; H, 4.12; N, 9.35.

2-Oxo-7-chlorindoline;

2-Oxo-5-methoxyindoline; m.p. 150°–151°C.
Anal. Calcd for $C_9H_9NO_2$:
C, 66.25; H, 5.56; N, 8.58; O, 19.61.
Found: C, 66.12; H, 5.52; N, 8.30; O, 19.83.

2-Oxo-6-trifluoromethylindoline; m.p. 176°–179°C.
Anal. Calcd for $C_9H_6F_3NO$:
C, 53.74; H, 3.00; N, 6.96

Found: C, 54.03; H, 3.23; N, 6.78.

2-Oxo-7-methylindoline; m.p. 201°–203°C.

Anal. Calcd for C_9H_9NO:

C, 73.45; H, 6.16; N, 9.52; O, 10.87.

Found: C, 73.32; H, 6.16; N, 9.47; O, 10.73.

2-Oxo-7-trifluoromethylindoline; m.p. 203°–206°C.

2-Oxo-5-methylindoline; m.p. 179°–180°C.

Anal. Calcd for C_9H_9NO:

C, 73.45; H, 6.16; N, 9.52; O, 10.87.

Found: C, 73.49; H, 6.17; N, 9.52; O, 10.77.

2-Oxo-5-fluoroindoline; m.p. 134°–135°C.

Anal. Calcd for C_8H_6FNO:

C, 63.58; H, 4.00; N, 9.27;

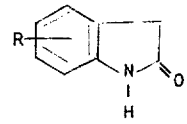
Found: C, 63.76; H, 4.12; N, 9.41.

milligrams of test compound per milliliter. The individual weights of three canaries are determined, and a predetermined amount of the acacia suspension, measured in milligrams of test compound per kilogram of body weight of the canary, is orally injected. The birds are placed in a lighted area and observed for a period of one hour, and the length of time that each bird sleeps is noted.

In the Table following is provided the tranquilizing activity of the oxo-indolines which are used in the method and are present in the composition of this invention. This activity is determined by means of the aforedescribed test procedure.

TABLE

ACTIVITY OF 2-OXO-INDOLINES



Milligrams per kilogram weight of canary[a]

	160		80		40		20		10		5		2.5	
R	No.	Min.	No.	Min.	No.	Min.	No.	Min.	No.	Min.	No.	Min.	No.	Min.
6-Methyl	2	23	3[b]	18	2	30	1	10	1	2	-	-	1	3
6-Methoxy	1	3	3	15	0	-	-	-	-	-	-	-	-	-
4-Methyl	-	-	3	28	1	8	-	-	-	-	-	-	-	-
6-Chloro	3	37	3	35	0	-	-	-	-	-	-	-	-	-
4-Chloro	3	45	1	12	0	-	-	-	-	-	-	-	-	-
6-Fluoro	3	42	1	7	3	13	0	-	-	-	-	-	-	-
5-Methoxy	3	17	1	17	1	10	0	-	-	-	-	-	-	-
7-Methyl	3	55	6[b]	33	2	17	2[b]	6	0	-	-	-	-	-
5-Methyl	1	7	2	5	0	-	-	-	-	-	-	-	-	-
5-Fluoro	3	28	3	35	3	20	0	-	1	2	1	5	-	-
5-Chloro	-	-	2	18	0	-	-	-	-	-	-	-	-	-
7-Chloro	-	-	3	37	0	-	-	-	-	-	-	-	-	-
6-Trifluoromethyl	-	-	3	48	1	22	1	12	-	-	-	-	-	-
7-Trifluoromethyl	3	22	3[b]	18	2	20	-	-	-	-	-	-	-	-

Footnotes--

a. "No." refers to the number of canaries of the test group in which sleep was induced. Unless otherwise indicated, a test group comprises three canaries. "Min." refers to the combined total minutes of sleep which were recorded divided by the number of canaries in the group.

b. Test group is composed of six canaries.

The activity of the oxo-indolines as tranquilizers can be demonstrated by their hypnotic effect on canaries. In this activity evaluation, the test compound is placed into a 5 percent aqueous acacia suspension in an amount sufficient to provide a mixture containing 8

I claim:

1. A pharmaceutical composition for relieving a condition associated with anxiety and tension comprising a therapeutically effective dose of an oxo-indoline of the formula

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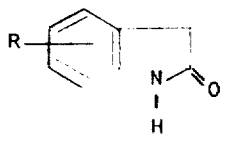

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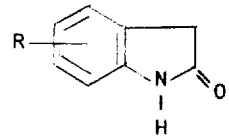

in which R is C_1–C_3 alkyl, C_1–C_3 alkoxy, halo, or trifluoromethyl, in association with a pharmaceutical carrier.

2. Composition of claim **1** which comprises from about 0.5 to about 500 milligrams of the indoline in association with a pharmaceutical carrier.

3. Composition of claim **1**, in which R is methyl.

4. Composition of claim **1**, in which R is methoxy.

5. Composition of claim **1**, in which R is halo.

6. Composition of claim **5**, in which R is chloro or fluoro.

7. Composition of claim **1**, in which R is trifluoromethyl.

8. A method of treating a patient to relieve anxiety and tension, which comprises administering to said patient a pharmaceutically effective amount of an oxoindoline of the formula

in which R is C_1–C_3 alkyl, C_1–C_3 alkoxy, halo, or trifluoromethyl.

9. Method of claim **8**, in which the indoline is administered at the rate of about 0.5 to about 500 milligrams per day.

10. Method of claim **9**, in which the indoline is administered at a rate of about 2 to about 200 milligrams per day.

11. Method of claim **8**, in which the indoline is administered orally.

12. Method of claim **8**, in which R is methyl.

13. Method of claim **8**, in which R is methoxy.

14. Method of claim **8**, in which R is halo.

15. Method of claim **14**, in which R is chloro or fluoro.

16. Method of claim **8**, in which R is trifluoromethyl.

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