Patented May 9, 1950 2,507,337

UNITED STATES PATENT OFFICE

2,507,337

1,5-DIALKYL TETRAZOLES AND PREPARATION THEREOF

Edward K. Harvill, Orange, and Robert M. Herbst, Short Hills, N. J., assignors to E. Bilhuber, Inc., Orange, N. J., a corporation of New Jersey

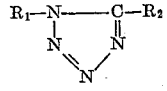
No Drawing. Application June 12, 1946, Serial No. 676,344

7 Claims. (Cl. 260—308)

1

This invention pertains to new and useful tetrazole compounds having valuable therapeutic properties therein, and to their preparation.

The new compounds of our invention comprise the 1,5 substituted, dialkyl tetrazoles of the general formula:



wherein R_1 and R_2 are aliphatic alkyl groups, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, etc., or cycloalkyl groups, such as cyclohexyl, cyclopentyl, etc.; and, more specifically, wherein one of the substituents R_1 or R_2 is preferably an alkyl group of low order, such as methyl or ethyl, while the remaining substituent is an alkyl group of higher order, such as propyl, butyl, isopropyl, isobutyl, cyclohexyl, etc.

We have discovered, in accordance with an important aspect of our invention, that the 1,5 dialkyl tetrazoles of the character aforesaid are valuable therapeutic agents having marked pharmacological effects on the central nervous system, which vary in character and degree with the magnitudes and character of the alkyl substituents R_1 and R_2, and especially with the relative magnitudes of these substituents and their relative locations on the tetrazole ring.

Thus, we have discovered that whereas the parent compound, tetrazole, is substantially devoid of pharmacological action even when administered in large doses, the simplest of the 1,5 dialkyl tetrazoles, viz., 1,5 dimethyl tetrazole, is very mildly sedative in its action. Also that if the substituent R_1 attached to the nitrogen atom is kept relatively small, for example, methyl or ethyl, while the substituent R_2 attached to the carbon atom is increased to a higher order, for example, propyl, butyl, etc., the sedative or depressant action of the compound increases markedly in intensity, assuming a maximum intensity when the R_2 alkyl substituent is of the order of butyl, amyl or cyclohexyl. On the other hand, if the relative magnitudes of the substituents R_1 and R_2 are increased in the reverse order, that is to say, if the substituent R_2 attached to the carbon atom remains small, i. e., methyl or ethyl, while the remaining substituent R_1 attached to the nitrogen atom, is increased to a higher order, for example, propyl, butyl, etc., the pharmacological action of the compound changes from sedative or depressant in character to that of a stimulant, in which the stimulant action increases in intensity with the magnitude of the R_1 substituent until a maximum stimulating action is obtained when R_1 is of the order of isobutyl or cyclohexyl.

Thus, the invention provides a series of basically similar, 1,5 alkyl substituted, tetrazole compounds, the pharmacological effects of which vary gradually in one direction from mildly sedative to intensely sedative or depressant in action, and which vary gradually in the opposite direction from mildly stimulating to intensely stimulating in action for a given dosage. These new compounds are characterized not only by a high level of potency as central nervous and respiratory stimulants or depressants, but are further characterized by unusually prolonged action thereof.

2

It is to be emphasized that it is the relative magnitudes of the substituents R_1 and R_2 on which the intensity of the depressant or stimulant activity depends. For example, the highly active stimulant, 1-isobutyl-5-methyl tetrazole is almost completely inactivated by replacing the methyl group with an isobutyl group. Similarly, the extremely active 1-cyclohexyl-5-methyl tetrazole undergoes a decrease in potency when the methyl group is replaced by an ethyl group, and a substantially complete loss of activity when the methyl group is replaced by isobutyl or cyclohexyl. That is to say, if the substituents R_1 and R_2 are of the same order of magnitude, for example, both are butyl, isobutyl, cyclohexyl, etc., the therapeutic action of the resulting compound becomes substantially nil.

For a given number of carbon atoms in the alkyl substituents for R_1 or R_2, the branched chain groups, such as isopropyl, isobutyl, cyclohexyl, etc., impart to the resulting compound a more potent stimulant or depressant action than do the straight chain alkyl groups, such as propyl, butyl, etc. The substitution of aromatic groups, such as phenyl, for alkyl groups in R_1 or R_2 markedly decreases the potency of the compound, which is thereby rendered only mildly stimulating or depressant in action.

The new compounds of the invention may be prepared from appropriate monosubstituted acid amides of the general formula, R_1NHCOR_2, where R_1 and R_2 are aliphatic alkyl and cyclo-alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclohexyl and cyclopentyl.

In accordance with the invention, such amides are treated, in an indifferent or inert organic solvent, with phosphorus pentachloride, in connection with which we have found it be of the utmost importance for the successful synthesis of these new tetrazoles to keep the temperature of the reaction mixture below 50° C. At higher temperatures monosubstituted acid amides in which a hydrogen atom is present on the alpha-carbon atom of the acidic portion, tend to halogenate on this alpha-carbon atom on treatment with phosphorus halides. These halogenated compounds are highly reactive and tend to condense and eliminate hydrogen chloride to form complex products at temperatures above 50° C.

At temperatures below 50° C. treatment of the acid amide with phosphorus pentachloride favors the formation of the imido-chloride which without isolation on further treatment with hydrazoic acid or sodium azide leads to the production of the desired tetrazole.

The following examples are illustrative:

EXAMPLE I

1-cyclohexyl-5-ethyl tetrazole

To a cooled solution of 80 grams of N-cyclohexyl propionamide in 500 cc. of anhydrous ether, 106 grams of phosphorus pentachloride was added portion-wise. The ether was removed from a solid mass of crystals under reduced pressure by warming the reaction mixture to 40° C. The residue was treated with 500 cc. of benzene containing 25 grams of hydrazoic acid and the mixture allowed to stand at room temperature for fifteen hours. The solution was then refluxed until hydrogen chloride evolution had ceased and the solvent was removed under reduced pressure. The residue was refluxed with aqueous sodium hydroxide and from the cooled solution 72 grams of 1-cyclohexyl-5-ethyl tetrazole was collected by filtration, M. P. 111–113° C. Recrystallization from water gave a white crystalline product, M. P. 112–112.5° C.

EXAMPLE II

1-cyclohexyl-5-methyl tetrazole

To a solution of 100 grams of N-cyclohexyl-acetamide in 500 cc. of benzene, 147 grams of phosphorus pentachloride was added in small portions. The solution was cooled to keep the temperature below 50° C. and moderate the vigorous reaction. To the cooled solution, 34 grams of hydrazoic acid in benzene was added and after one hour the solution was refluxed, until hydrogen chloride evolution had ceased. The solvent was removed under reduced pressure and the residue was refluxed in water. From the cooled solution, 1-cyclohexyl-5-methyl tetrazole separated as light yellow needles weighing 79 grams after drying. After recrystallizing twice from water, 60 grams of white crystalline product, melting at 124–124.5° C., was obtained.

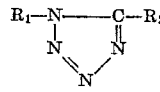
By application of the methods disclosed in the foregoing examples to the appropriate mono-substituted acid amides, the following 1,5-dialkyl tetrazoles have been prepared:

Compound	M. P. (B. P.), °C.	Analysis Per Cent N	
		Calculated	Found
1,5-Dichlohexyl tetrazole	179.5–180	23.93	23.88
1,5-Diisobutyl tetrazole	(1)	30.77	30.42
1-Ethyl-5-cyclohexyl tetrazole	84–86	31.11	31.24
1-Cyclohexyl-5-isobutyl tetrazole	78.5–79	26.92	26.91
1-Cyclohexyl-5-ethyl tetrazole	112–112.5	31.11	31.14
1-Methyl-5-cyclohexyl tetrazole	97–98	33.73	33.74
1-Isobutyl-5-cyclohexyl tetrazole	81–82	26.92	26.74
1-Cyclohexyl-5-methyl tetrazole	124–124.5	33.73	33.84
1-Cyclohexyl-5-propyl tetrazole	79–80	28.87	28.91
1-Cyclohexyl-5-isopropyl tetrazole	85–86	28.8	28.90
1-Cyclohexyl-5-n-butyl tetrazole	43.5–45.0	26.92	27.09
1-Cyclopentyl-5-methyl tetrazole	62–62.5	36.60	36.84
1-Hexahydrobenzyl-5-methyl tetrazole.	87–88	31.11	31.26
1-Isobutyl-5-methyl tetrazole	45–45.5	40.00	39.70

(1) (161–162.5/8 mm. Hg).

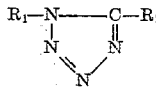
We claim:

1. The therapeutically active tetrazole compound of the general formula:



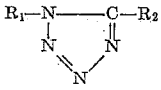
wherein one of the radicals R_1 and R_2 is selected from the group consisting of methyl and ethyl, and the remaining radical is selected from the group consisting of, saturated, straight and branched chain alkyl radicals having three and four carbon atoms, and cycloalkyl radicals of five and six carbon atoms.

2. The therapeutically sedative tetrazole compound of the general formula:



wherein R_1 is selected from the group consisting of methyl and ethyl, and R_2 is selected from the group consisting of saturated, straight and branched chain alkyl radicals of three and four carbon atoms, and cycloalkyl radicals of five and six carbon atoms.

3. The therapeutically stimulating tetrazole compound of the general formula:



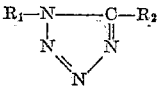
wherein R_2 is selected from the group consisting of methyl and ethyl, and R_1 is selected from the group consisting of saturated, straight and branched chain alkyl radicals of three and four carbon atoms, and cycloalkyl radicals of five and six carbon atoms.

4. The therapeutically active compound 1-cyclohexyl-5-methyl tetrazole.

5. The therapeutically active compound 1-cyclohexyl-5-ethyl tetrazole.

6. The therapeutically active compound 1-isobutyl-5-methyl tetrazole.

7. The method of preparing tetrazole compounds of the general formula:



wherein R_1 and R_2 are alkyl radicals, which comprises: reacting a mono substituted acid amide of the general formul R_1NHCOR_2, with phosphorus pentachloride in an inert organic solvent in the absence of a basic catalyst at a temperature below 50° C., and subsequent treatment, without isolation of the intermediates, with a member selected from the group consisting of hydrazoic acid and sodium azide.

EDWARD K. HARVILL.
ROBERT M. HERBST.

REFERENCES CITED

The following references are of record in the file of this patent:

UNITED STATES PATENTS

Number	Name	Date
1,943,148	Scheuing	Jan. 9, 1934

OTHER REFERENCES

Chemical Abstract, vol. 40, page 6656 citing Gross et al., Jr., Pharmacology and Experimental Therapeutics, vol. 87, pp. 299–305 (1946).