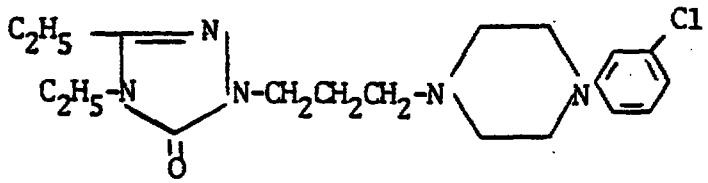
2-PHENOXYALKYL-1,2,4-TRIAZOL-3-ONE ANTIDEPRESSANTS

The present invention relates to 1,2,4,-triazole heterocyclic carbon compounds and to their preparation. More particularly, the invention relates to 2-[3-[4-(halo-phenyl)-1-piperazinyl]propyl]-5-ethyl-4-(phenoxyalkyl)-2H-1,2,4,-triazol-3(4H)-ones, 4-[3-[4-(halo-phenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-2-(phenoxyalkyl)-3H-1,2,4,-triazol-3-ones.

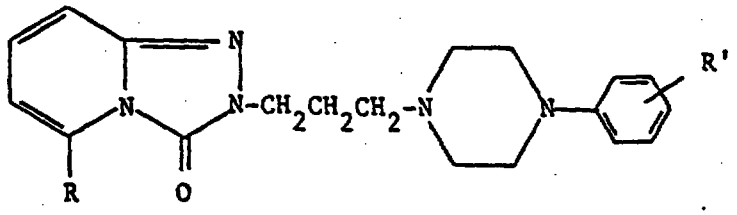
U.S. Patent 3,857,845 to G. Palazzo describes the compound 1-[3-(4-meta-chlorophenyl-1-piperazinyl)propyl]-3,4-diethyl-2-1,2,4,-triazolin-5-one depicted structurally below.



Alternatively, the compound can be named 2-[3-[4-(3-chlorphenyl)-1-piperazinyl]propyl]-4,5-diethyl-2H-1,2,4-triazol-3(4H)-one, and is commonly called etoperidone.

Regarding utility, the '845 Palazzo patent discloses that etoperidone has pharmacological properties typical of tranquilizers including sedation, reduced activity towards the experimentor and lower motor activity. In addition, hypotensive and analgesic activity are reported with possible use as an antianxiety agent and tranquilizer in human therapy mentioned.

U.S. Patent 3,381,009 to G. Palazzo, et al., discloses 1,2,4-triazolo[4,3-a]pyridines of the following general formula

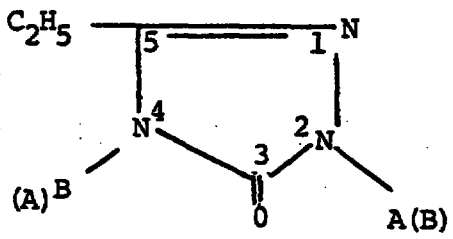


wherein R is hydrogen or methyl and R' is hydrogen, alkyl (1-4C), alkoxy (1-4C), or halogen. The compounds are said to exhibit tranquilizing action, hypotensive action, and analgesic action according to various animal tests. With respect to tranquilizing action, the pharmacological profile includes such behavioral effects as sedation, decrease in motor activity, hypotonia, high dose induced muscular non-coordination and ataxia, and inhibition of conditioned reflexes in the rat. According to the '009 patent, data relative to behavioral, adrenolytic and anti-serotonin effects indicate that the compounds resemble major tranquilizers, such as chlorpromazine more than minor ones such as meprobamate. Pharmacological properties of one compound in particular, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one, have been described in more detail

(11)

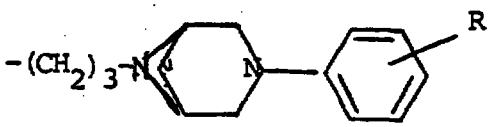
by Silvestrini, et al., International Journal of Neuropharmacology, 7, 587-599 (1968). The aforementioned compound, commonly known as trazodone, has been studied extensively in man and is considered to be an antidepressive equivalent in effectiveness to imipramine but with fewer side effects (Fabre, et al., Current Therapeutic Research, 25, 827-834 (1979)).

Broadly described, the present invention is concerned with piperazinylalkyl-1,2,4-triazol-3-ones characterized by Formula I

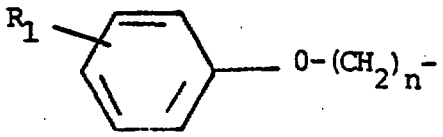


(I)

wherein A is a radical of the formula



and B is a radical of the formula



and,

(12)

wherein n is the integer 2-4, R is halogen, R_1 is hydrogen, halogen or alkoxy, and pharmaceutically acceptable salts thereof. The term "halogen" or halo as used herein comprehends fluorine, iodine and most preferably bromine and chlorine. The term alkoxy as used herein comprehends from 1 to 4 carbon atoms, such as methoxy, ethoxy, tert-butoxy and the like.

The pharmaceutically acceptable acid addition salts are those in which the anion does not contribute significantly to the toxicity or pharmacological activity of the salt and, as such, they are the phamacological equivalents of the bases of Formula I. They are generally preferred for medical usage. In some instances, they have physical properties which makes them more desirable for pharmaceutical formulation purposes such as solubility, lack of hygroscopicity, compressibility with respect to tablet formation and compatibility with other ingredients with which the substance may be used for pharmaceutical purposes. The salts are made by reaction of the base of Formula I with the selected acid preferably by contact in solution. They may also be made by metathesis or treatment with an ion exchange resin under conditions in which the anion of one salt of the substance of the Formula I is replaced by another anion under conditions which allow for separation of the desired species such as by precipitation from solution or extraction into a solvent, or elution from or retention on an ion exchange resin. Pharmaceutically acceptable acids for the purposes of salt formation of the substances of Formula I include hydrochloric, hydrobromic, hydroiodic, citric, acetic, benzoic, mandelic, phosphoric, nitric, mucic, isethionic, palmitic, heptanoic, and others.

(13)

In its most preferred embodiment, the present invention provides the compounds of Formula I wherein R is meta-chloro, R^1 is hydrogen and n is the integer 2.

The Formula I compounds are useful pharmacological agents with psychotropic properties. In this regard, they exhibit selective central nervous system effects associated with antidepressant activity according to conventional in vivo test systems such as those listed below.

Behavioral Test	Reference
Suppression of conditioned avoidance response (CAR)	Albert, et al., Pharmacologist, 4, 152 (1962).
Prevention of reserpine ptosis in mice (antidepressant)	Niemegeers, Industrial Pharmacology, Vol. 2 - Antidepressants, Ed. by S. Fielding and H. Lal, pp. 73-98, Futura, New York, N.Y., (1975).
Potentiation of alcohol Hypnois in the mouse (sedative)	- - -

In these tests, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]-propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one suppressed CAR in the rat and prevented but did not reverse reserpine ptosis in the mouse. Such activity is characteristic of most clinically useful antidepressant agents. Sedation is a common side effect of antidepressants. In this regard, compound Ia exhibited only minimal activity in potentiating alcohol hypnosis in the mouse which is indicative of a relative lack of this adverse reaction.

(14)

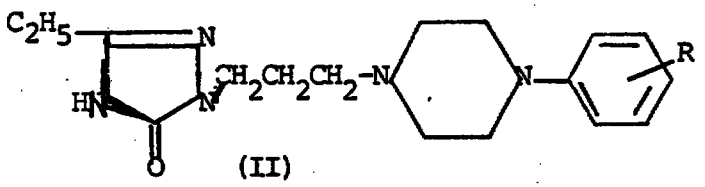
As further indication of the psychotropic activity and specificity of the instant compounds, state of the art in vitro central nervous system receptor binding methodology can be employed. Certain compounds (commonly referred to as ligands) have been identified which preferentially bind to specific high affinity sites in brain tissue dealing with psychotropic activity or potential for side effects. Inhibition of radiolabeled ligand binding to such specific high affinity sites is considered a measure of a compound's ability to affect corresponding central nervous system function or cause side effects in vivo.

The following tests, as well as others, can be employed in developing a profile of the psychotropic activity of the instant compounds.

Receptor Binding Assay	Reference
Dopamine	Burt, et al., Molec. Pharmaccl., 12, 800 (1976); Science, 196, 326 (1977); Creese, et al, Science, 192, 481 (1976).
Cholinergic	Yamamura, et al., Proc. Natn. Acad. Sci. USA 71 1725 (1974).
Alpha-receptor	Crews, et al., Science 202: 322 (1978). Rosenblatt, et al., Brain Res. 160: 186 (1979) U'Prichard, et. al Science 199: 197 (1978) U'Prichard, et. al Molec. Pharmacol. 13: 454 (1977).
Serotonin Type 2	Peroutka and Snyder, Molec. Pharmacol. 16: 687 (1979)

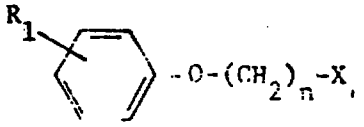
According to the foregoing assays, compounds of the formula I wherein R is meta-chloro and R is hydrogen inhibit serotonin binding and was relatively inactive with respect to dopamine receptor binding, cholinergic receptor binding, and alpha-receptor binding. The latter is particularly significant in that drugs with high affinity for alpha-receptors relative to serotonin type 2 receptors are likely to cause side effects such as sedation and blood pressure lowering. Thus, the instant compounds and particularly the above-mentioned most preferred embodiments are considered improved antidepressants with minimal side effect potential.

According to the present invention, the 2-piperazinylalkyl-1,2,4-triazol-3-ones characterized by Formula I are obtained by the following process which comprises treating a 2-piperazinylalkyltriazolone of Formula II



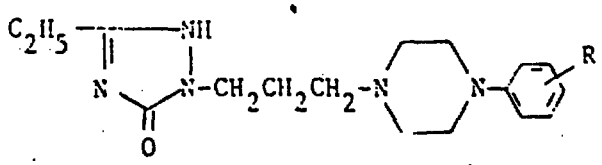
(II)

wherein R is halogen attached in the 2,3 or 4 position of the phenyl ring with a suitable alkali metal base such as sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate to form an alkali metal salt thereof; and then alkylating the Formula II alkali metal salt with a phenoxyalkylhalide of Formula VII wherein R_1 is as defined above, n is the integer 2-4 and "X" comprehends halogen, preferably chlorine or bromine, or a suitable leaving group such as sulfate, phosphate, tosylate, mesylate, and the like



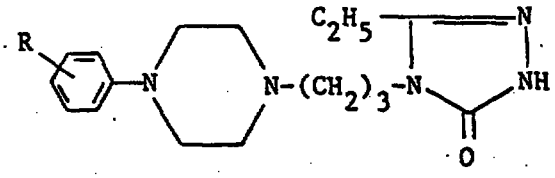
(VII)

It is to be understood that Formula II depicts a tautomer of a compound [illegible] Formula II'.



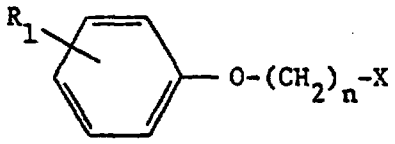
(II')

The 4-piperazinylalkyl-1,2,4-triazol-3-ones characterized by Formula I are obtained by the following process which comprises reacting a 4-piperazinylalkyltriazolone of Formula IIa



(IIA)

wherein R is halogen attached in the 2, 3 or 4 position of the phenyl ring with a phenoxyalkylhalide of Formula (VII)



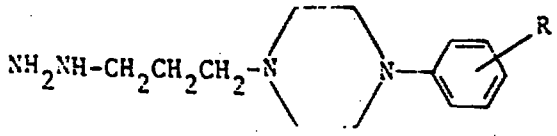
(VII)

wherein R_1 is as defined above, n is the integer 2-4 and "X" comprehends halogen, preferably chlorine or bromine, or a suitable leaving group such as sulfate, phosphate, tosylate, mesylate, and the like, in the presence of a suitable alkali metal base such as sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate in a reaction inert solvent such as xylene or acetonitrile and the like.

(17) Standard laboratory procedures are employed in carrying out the foregoing reaction such as those described for the alkylation step of the Gabriel synthesis - S. Gabriel, Ber. 20, 2224 (1887). In the present case, the reactants are combined in an inert reaction solvent at temperatures ranging from about 50°C. to 200°C. Acetonitrile and xylene are particularly preferred solvents for carrying out the reaction but other solvents which do not adversely affect the reaction or reactants can be employed. In this regard, solvents such as benzene, toluene dimethylformamide, n-butanol, and the like are suitable. The reaction period varies to some extent depending on solvent and temperature selected. For instance, at lower temperatures, long reaction periods are needed while at higher temperatures, alkylation is completed in a shorter time. In the case of acetonitrile or xylene, optimum yields are obtained with a reaction period of 8 to 68 hours.

A preferred process for preparing Formula I products comprises reacting a piperazinylalkyltriazolone of Formula II (or IIa) with a phenoxyalkylhalide of Formula VII in the presence of an alkali metal carbonate such as potassium carbonate or sodium carbonate in acetonitrile.

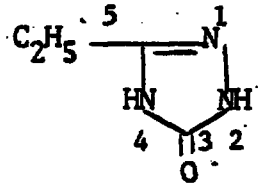
The Formula II (2-) piperazinylalkyltriazolone intermediates are preferably obtained by alkylating hydrazine with a 1-(halophenyl)-4-(3-halopropyl)piperazine to provide a 1-(halophenyl)-4-(3-hydrazinopropyl)piperazine of Formula III



(III)

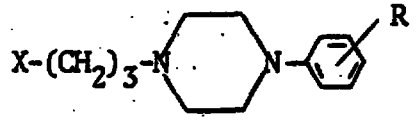
which is then condensed with N-ethoxycarbonylthiopropionamide ($CH_3CH_2\overset{S}{\overset{\|}{C}}-NH-\overset{O}{\overset{\|}{C}}OC_2H_5$) in a reaction inert solvent at elevated temperature. Alkanols, such as ethanol, are particularly preferred as solvents with the reaction conveniently carried out atreflux temperature. Other suitable solvents include acetone, acetonitrile, ethylacetate, dimethylformamide, ethers such as tetrahydrofuran and the like.

The Formula IIa 4-piperazinylalkyltriazolone intermediates are prepared by heating N-ethoxycarbonylthiopropionamide with hydrazine in ethanol to provide the triazolone compound of Formula IV



(IV)

which is then alkylated with a 1-(halophenyl)-4-(3-halopropyl)-piperazine of Fomula V

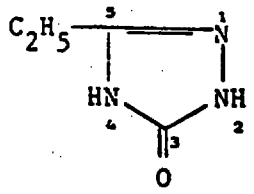


(V)

wherein R is halogen and X comprehends halogen, preferably chlorine or bromine, or a suitable leaving group such as sulfate, phosphate, tosylate, mesylate, and the like, in the presence of a suitable alkali metal base such as sodium carbonate, potassium carbonate, potassium hydroxide, sodium hydroxide and the like in a reaction inert solvent. Laboratory procedures and solvents (preferably acetonitrile) previously disclosed as operable for the alkylation of Formula IIa intermediates with Formula VII phenoxyalkyl halides are employed.

(19)

Another operable procedure for preparing Formula II and IIa intermediates comprises heating N-ethoxycarbonylthiopropionamide with hydrazine in ethanol to provide the triazolone compound of Formula IV

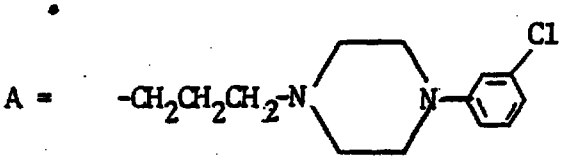


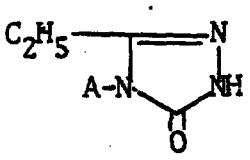
(IV)

which is then alkylated with a 1-(halophenyl)-4-(3-halopropyl)piperazine compound in xylene at reflux temperature. Compared to the previously described preparation of Formula II intermediates, this method is not as satisfactory in that the triazolone (IV) is alkylated indiscriminately at "two and four" positions resulting in lower yields of the desired piperazinylalkyltriazolone (II). For example, reaction of triazolone (IV) with 1-(3-phenyl)-4-(3-chloropropyl)piperazine in refluxing xylene affords the following compounds (isolated as hydrochloride salts) as secondary products in addition to the desired Formula (II) piperazinyl-alkyltriazolone intermediate wherein R is meta-chloro.

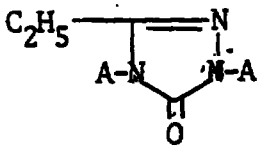
(29)

Secondary Products

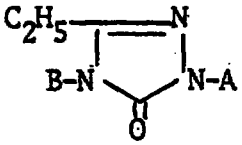
A =  . HCl

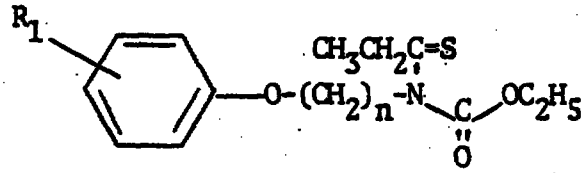


4-[3-[4-(3-Chlorophenyl)-1-piperazinyl]-propyl]-5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one hydrochloride; m.p. 210-212°C. (dec.)



2,4-bis-[3-[4-(3-Chlorophenyl)-1-piperazinyl]-propyl]-5-ethyl-2H-1,2,4-triazol-3(4H)-one hyrdochloride; m.p. 206-208°C. (dec.)

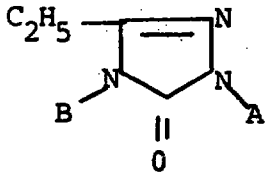
An alternate process for preparing a compound of Formula  comprises condensing a Formula III 1-(halophenyl)-4-(3-hydrazino-propyl)piperazine with a N-phenoxyethyl-N-ethoxycarbonylthiopropion-amide of Formula (V) wherein R_1 is as defined above and n is 2-4.



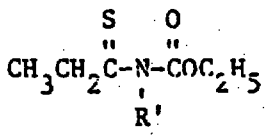
(V)

The condensation is carried out in a suitable reaction inert solvent such as ethanol as previously described for the preparation of the Formula (II) piperazinylalkyltriazolones. The Formula V intermediate can be obtained by standard methods such as condensing methyl dithio-propionate with a N-(phenoxyalkyl)ethylcarbonate under basic conditions or alkylating N-ethoxycarbonylthiopropionamide with a phenoxyalkyl-halide of Formula VII in the presence of an alkali metal base.

The procedures hereinabove described for preparing compounds of the formula

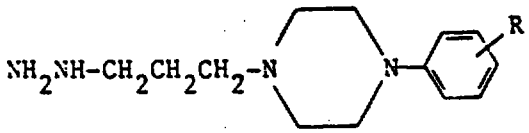


constitutes a unitary process which comprises condensing an amide of the Formula VI



(VI)

wherein R' is hydrogen or R_1-phenoxyalkyl of 2 to 4 carbon atoms with a 1-(halophenyl)-4-(3-hydrazinopropyl)piperazine of Formula III

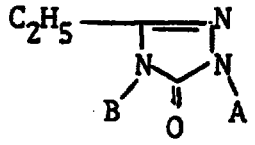


(III)

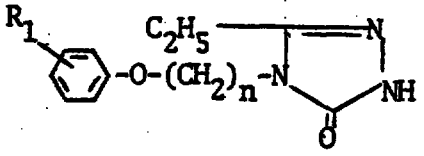
wherein R is halogen in a reaction inert solvent at elevated temperatures to provide compounds of Formula I when R' is R_1-phenoxyalkyl and compounds of Formula II when R' is hydrogen and thereafter alkylating a Formula II compound with a phenoxyalkyl halide of Formula VII in the presence of an alkali metal base.

(22)

A still further preferred process for preparing a compound of the formula

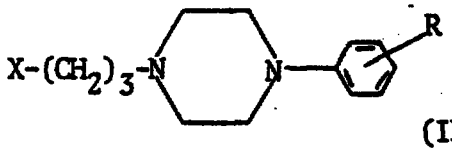


comprises alkylating a Formula VIII phenoxyalkyltriazolone



(VIII)

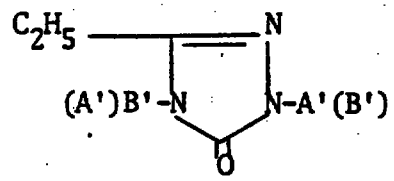
wherein R_1 is hydrogen, halogen or alkoxy, and n is the integer 2-4 with a 1-(halophenyl)-4-(3-halopropyl)piperazine of Formula IX



(IX)

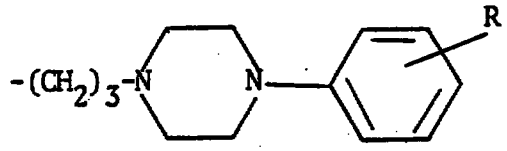
wherein R is halogen and X comprehends halogen, preferaly chlorine or bromine, or a suitable leaving group such as sulfate, phosphate, tosylate, mesylate, and the like, in the presence of a suitable alkali metal base such as sodium carbonate, potassium carbonate, potassium hydroxide and preferably sodium hydroxide in a reaction inert solvent. The term "reaction inert solvent" refers to any protic or aprotic solvent or diluent which does not enter into the reaction to any substantial degree. Laboratory procedures and solvents previously disclosed as operable for the alkylation of Formula II intermediates with Formula VII phenoxyalkyl halides are employed, In the instant case, alkanols, particularly isopropanol, are preferred.

The aforementioned preferred processes for preparing compounds of Formula I from triazolone intermediates of Formula II and VIII can be viewed as embodiments of a unitary process which comprises alkylating a compound of Formula X

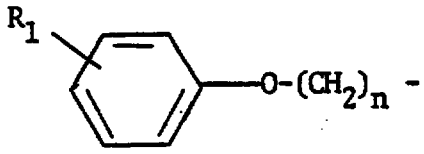


(X)

wherein A' is hydrogen or a 1-(halophenyl)-4-(3-halopropyl)piperazine radical



B' is hydrogen or the phenoxyalkyl radical



in which "R_1" is as defined above, "n" is the integer 2 to 4 and one of "A" or "B" must be hydrogen with an alkylating agent of Formula VII or IX.

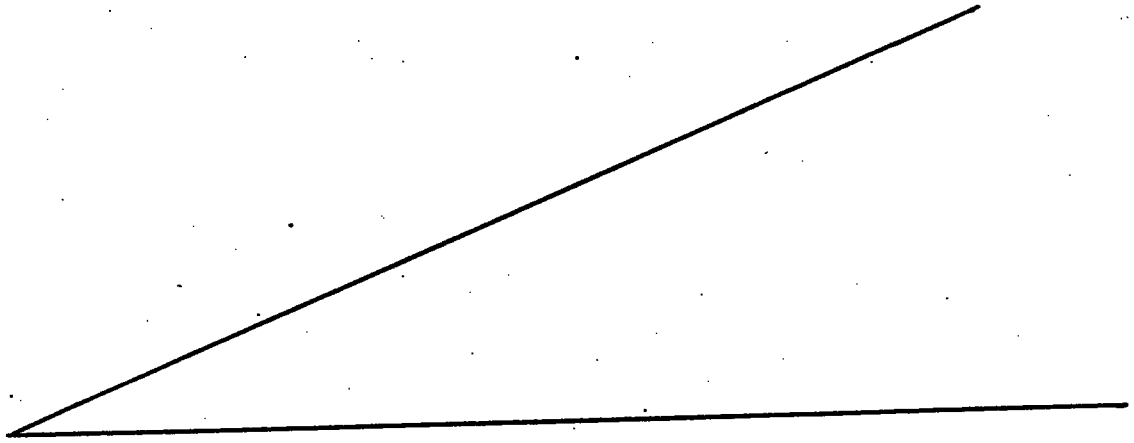
The compounds and composition of the invention can be used for treating a mammal afflicted with depression by ———— administering systemically to said mammal a therapeutically effective antidepressant amount of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof. An effective dose ranges from 0.01 to 40 mg/kg of body weight with the dosage on dependant on effects sought, manner of administration, and to some extent with the particular compound selected. Systemic administration refers to oral, rectal and parenteral (i.e. intramuscular, intravenous and subcutaneous). Generally, it will be found that when a compound of the present invention is administered orally, a larger quantity of the active agent is required to produce the same effect as a smaller quantity given parenterally. In accordance with good clinical practice, it is preferred to adminster the instant compounds at a concentration

level that will produce effective antidepressant effects without causing any harmful or untoward side effects.

The compounds of the present invention may be administered for antidepressant purposes either as individual therapeutic agents or as mixtures with other therapeutic agents. Therapeutically, they are generally given as pharmaceutical compositions comprised of an antidepressant amount of a compound of Formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Pharmaceutical compositions which provide from about 1 to 500 mg. of the active ingredient per unit dose are preferred and are conventionally prepared as tablets. lozenges. capsules, powders, aqueous or oily suspensions, syrups, elixirs and acqueous solutions.

The nature of the pharmaceutical composition employed will, of course, depend on the desired route of administration. For example, oral compositions may be in the form of tablets or capsules and may contain conventional excipeints such as binding agents (e.g. syrup, acacia, gelatin. sorbitol, tragacanth, or polyvinylpyrrolidone), fillers (e.g. lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine), lubricants (e.g. magnesium stearate, talc, polyethyleneglycol or silica), disintegrants (e.g. starch) and wetting agents (e.g. sodium lauryl sulfate). Solutions or suspensions of a Formula I compound with conventional pharmaceutical vehicles are employed for parenteral compositions such as an aqueous solution for intravenous injection or an oily suspension for intramuscular injection.

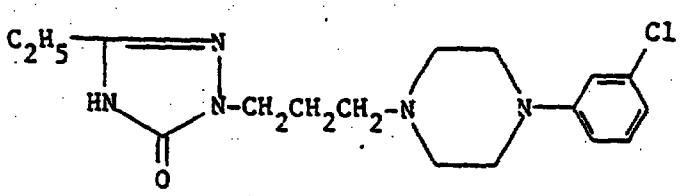
The following non-limiting examples illustrate the process and products of this invention. Nuclear magnetic responance (NMR) spectral characteristics refer to chemical shifts down field (δ).



expressed as parts per million (ppm) versus tetramethylsilane as reference standard. The relative area reported for the various shifts corresponds to the number of hydrogen atoms in the individual substituent and the nature of the shifts as to multiplicity is reported as broad singlet (bs), multiplet (m), triplet (t), or quadruplet (q) with coupling constant reported where appropriate. The format is NMR (solvent): δ(relative area, multiplicity, J value). Abbreviations employed are DMSO-d_6 (deuterodimethylsulfoxide), IR (infrared), and KBr (potassium bromide).

EXAMPLE 1

2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]-propyl]-5-ethyl-1H-1,2,4-triazol-3(2H)-one*(IIa)



(a) 1-(3-Chloropropyl)-4-(3-chlorphenyl)piperazine Hydrochloride.- A 50% sodium hydroxide solution (430.6 g., 5.333 mole) is added dropwise to a stirred solution of 1-(3-chlorophenyl)piperazine hydrochloride (502.0 g., 2.153 mole) and 1-bromo-3-chloropropane (339.0 g., 2.153 mole) in 435 ml. water and 535 ml. acetone while maintaining temperature of 0-10°C. Stirring is continued for a 16 hr. period at room temperature and the upper organic phase then separated and concentrated under reduced pressure. The remaining residual oil is taken up in 500 ml. acetone, filtered and the filtrate concentrated under reduced pressure to an oily residue which is dissolved in boiling dilute hydrochloric acid (1.67 liter water plus

*Alternately named 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one.

280 ml. concentrated HCl, 3.36 mole). The oil which initially separates from the cooled acid solution, solidifies on standing and is collected, rinsed with cold water and air dried. Crystallization of this material from water employing activated charcoal affords 438.4 g. (66%) of 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine hydrochloride, m.p. 196.5-198.5°C.

(b) 1-(3-Chlorophenyl)-4-(3-hydrazinopropyl)piperazine.- Hydrazine hydrate (10.7 g., 0.184 mole) in 20 ml. of ethanol is added slowly to 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine hydrochloride (9.29 g., 0.03 mole) in 20 ml. of ethanol. After refluxing the mixture for a 3 hr. period, the solvent is removed under reduced pressure and 20 ml. of water added to the residue. A 50 ml. portion of tetrahydrofuran is added to the aqueous mixture which is then saturated with potassium hydroxide pellets employing ice bath cooling. The tetrahydrofuran phase is separated, dried over magnesium sulfate and concentrated under reduced pressure to afford 7.4 g. (92%) of 1-(3-chlorophenyl)-4-(3-hydrazinopropyl)piperazine employed without further purification in the following step.

(c) 2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-1H-1,2,4-triazol-3(2H)-one.- A solution of 1-(3-chlorophenyl)-4-(3-hydrazinopropyl)piperazine (19.6 g., 0.073 mole) in 90 ml. of ethanol is added to N-ethoxycarbonylthiopropionamide (12.13 g., 0.073 mole) in 30 ml. of ethanol. The mixture is refluxed for a 16 hr. period with evolution of hydrogen sulfide and then concentrated under reduced pressure. Crystallization of residual material from ethanol affords 18.3 g. (72%) of 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]-propyl]-5-ethyl-1H-1,2,4-triazol-3(2H)-one, m.p. 79-81°C.

Addition of ethanolic hydrogen chloride to a sample of the base in ethanol with precipitation of the salt with ether affords 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-1H-1,2,4-triazol-3(2H)-one hydrochloride, m.p. 165-167°C.

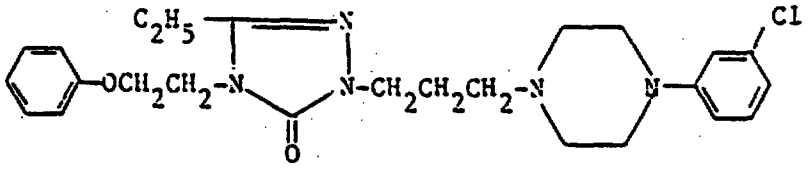
Anal. Calcd. for $C_{17}H_{24}ClN_5O \cdot HCl$: C, 52.86; H, 6.53; N, 18.13. Found: C, 52.72; H, 6.44; N, 17.96.

NMR (DMSO-d_6): 1,15 (3H,t, 7.3 Hz), 2.16 (2H,m), 2.43 (2H,q, 7.3 Hz), 3.18 (8H,m), 3.68 (4H,m), 6.89 (3H,m), 7.24 (1H,m), 11.49 (1H,bs).

IR (0.5% KBr, cm^{-1}): 770, 940, 1255, 1440, 1485, 1595, 1690, 2570, 2980.

EXAMPLE 2

2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one *



(a) Reaction in Xylene.- Sodium hydroxide (2.08 g., 0.052 mole) in 10 ml. of water is added slowly to 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-1H-1,2,4-triazol-3(2H)-one (18.2 g., 0.052 mole) in 150 ml. of warm ethanol with stirring. When mixing is complete, distillables are removed under reduced pressure. Ethanol is added to residual material and removed under reduced pressure and

*Alternately named 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one.

the process repeated until the sodium salt of 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-1H-1,2,4-triazol-3(2H)-one is obtained as a hard solid.

The sodium salt is pulverized, suspended in 200 ml. of xylene and mixed with phenoxyethyl bromide (10.4 g., 0.052 mole) in 20 ml. of xylene. The resulting mixture is refluxed with stirring for a 64 hr. period and the hot reaction mixture filtered. The filtrate is concentrated under reduced pressure and residual material taken up in ether. Insolubles are collected and the ether filtrate concentrated to afford 22.9 g. (94%) of 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one as the free base. Purification of the product is carried out by acidifying a solution of the free base in ethanol with ethanolic hydrogen chloride, and crystallization to afford hydrated (0.25 mole) 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one hydrochloride, m.p. 175-177°C. (30.7% yield).

Anal. Calcd. for $C_{25}H_{32}ClN_5O_2.HCl.1/4H_2O$: C, 58.77; H, 6.61; N, 13.71. Found: C, 58.61; H, 6148; N, 13.68.

NMR (DMSO-d_6) : 1.20 (3H,t 7.5 Hz), 2.16 (2H,m), 2166 (2H,q, 7.5 Hz), 3.27 (8H,m), 3174 (4H,m), 3.96 (2H,t), 4.17 (2H,t), 6.96 (6H,m), 7.29 (3H,m), 11.50 (1H,bs).

IR (0.5% KBr, cm^{-1}): 755, 940, 1235, 1440, 1490, 1595, 1710, 2580, 2940.

A sample of non-hydrated 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one hydrochloride obtained according to the above process melted at 175-177°C.

Anal. Calcd. for $C_{25}H_{32}ClN_5O_2 \cdot HCl$: C, 59.29; H, 6.57; N, 13.83. Found: C, 58.98; H, 6.44; N, 13.58.

NMR (DMSO-d_6): 1.20 (3H,t, 7.5 Hz), 2.14 (2H,m), 2.65 (2H,q, 7.5 Hz), 3.25 (8H,m), 3.72 (4H,m), 3.95 (2H,t), 4.16 (2H,t), 6.91 (6H,m), 7.25 (3H,m), 11.61 (1H,bs).

C^{13}NMR (DMSO-d_6): 9.65, 18.40, 22.90, 40.57, 41.89, 44.73, 50.31, 52.92, 64.95, 114.06, 114.30, 115.21, 119.12, 120.93, 129.53, 130.55, 133.94, 147.92, 150.78, 153.15, 157.87.

Ir (0.5% KBr, cm^{-1}): 750, 940, 1235, 1440, 1485, 1595, 1710, 2570, 2930.

(b) Reaction in Acetonitrile With Potassium Carbonate.- A mixture of 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-1H-1,2,4-triazol-3(2H)-one (15 g., 0.043 mole), phenoxyethyl bromide (8.62 g., 0.043 mole), potassium carbonate (11.9 g., 0.086 mole) and a trace of potassium iodide in 100 ml. of acetonitrile is refluxed for a 64 hr. period. The reaction mixture is filtered, the filtrate concentrated under reduced pressure and residual material taken up in ether and filtered. Concentration of the ethereal filtrate affords 18.35 g. (91%) of the free base product 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one. The free base is converted to the hydrochloride in ethanol employing ethanolic hydrogenchloride and crystallized from ethanol to afford a 53% yield of analytically pure 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl-2H-1,2,4-triazol-3(4H)-one hydrochloride, m.p. 175-177°C.

Anal. Calcd. for $C_{25}H_{32}ClN_5O_2 \cdot HCl$: C, 59.29; H, 6.57; N, 13.83. Found: C, 59.42; H, 6.68; N, 13.52.

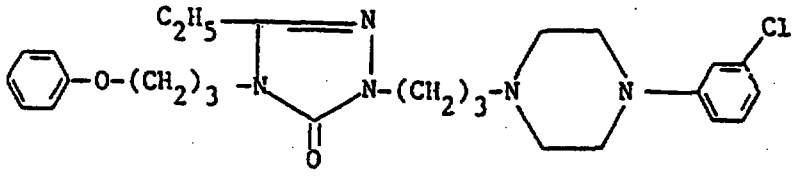
(30)

NMR (DMSO-d_6): 1.20 (3H,t, 7.5 Hz), 2.15 (2H,m), 2.65 (2H,q, 7.5 Hz), 3.25 (8H,m), 3.72 (4H,m), 3.95 (2H,t), 4.16 (2H,t), 6.93 (6H,m), 7.27 (3H,m), 11.61 (1H,bs).

IR (0.5% KBr, cm^{-1}): 755, 940, 1240, 1440, 1490, 1595, 1710, 2580, 2940.

EXAMPLE 3

2-[3-[4-(3-Chlorophenyl)-1-piperazinyl] propyl]-5-ethyl-2,4-dihydro-4-(3-phenoxypropyl)-3H-1,2,4-triazol-3-one



A mixture of 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-1H-1,2,4-triazol-3(2H)-one (3.86 g., 0.01 mole), 3-phenoxypropyl bromide (2.15 g., 0.01 mole), potassium carbonate (4.15 g., 0.01 mole) and a trace of potassium iodide in 50 ml. of acetonitrile is refluxed for a 65 hr. period. The reaction mixture is filtered, the filtrate concentrated under reduced pressure and residual material taken up in ether and filtered. Solvent is removed and further purification carried out by sequentially converting the free base to the hydrochloride salt and then to the free base which is chromatographically treated employing a silica column with methanol/chloroform eluant. Free base, obtained from the chromatographic separation, is converted to the hydrochloride salt in ethanol employing ethanolic hydrogen chloride to afford 1.17 g., (22% yield) of analytically pure 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(3-phenoxypropyl)-3H-1,2,4-triazol-3-one hydrochoride, m.p. 145-147°C.

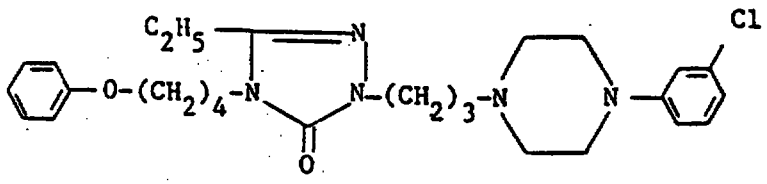
(31)

Anal. Calcd. for $C_{26}H_{34}ClN_5O_2 \cdot HCl$: C, 60.00; H, 6.78; N, 13.46. Found: 60.27; H, 6.82; N, 13.67.

NMR (DMSO-d_6): 1.15 (3H,t, 7.2 Hz); 2.10 (4H,m); 2.55 (2H,q, 7.2 Hz); 3.18 (6H,m); 3.75 (8H,m); 3.99 (2H,t, 6.0 Hz); 6.94 (6H,m); 7.27 (3H,m); 11.70 (1H,bs).

EXAMPLE 4

2-[3-[4-(3-Chlorophenyl)-1-piperazinyl] propyl]-5-ethyl-2,4-dihydro-4-(4-phenoxybutyl)-3H-1,2,4-triazol-3-one



A mixture of 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-1H-1,2,4-triazol-3-(2H)-one (3.86 g., 0.01 mole), 4-phenoxybutyl bromide (2.29 g., 0.01 mole), potassium carbonate (4.15 g., 0.01 mole) and a trace of potassium iodide in 50 ml. of acetonitrile is refluxed for a 65 hr. period. The reaction mixture is filtered, the filtrate concentrated under reduced pressure and residual material taken up in ether and filtered. Concentration of ethereal filtrate affords the free base. Conversion of the free base to the hydrochloride salt in ethanol with ethanolic hydrogen chloride and crystallization of the salt from ethanol affords analytically pure 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(4-phenoxybutyl)-3H-1,2,4-triazol-3-one hydrochloride, m.p. 152-154°C.

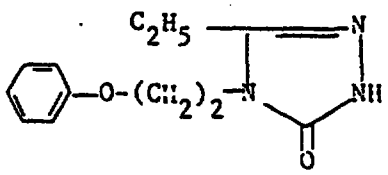
Anal. Calcd. for $C_{27}H_{36}ClN_5O_2 \cdot HCl$: C, 60.68; H, 6.98; N, 13.11. Found: C, 60.70; H, 6.86; N, 13.25.

(32)

NMR (DMSO-d_6): 1.19 (3H,t, 7.4 Hz); 1.74 (4H,m); 2.19 (2H,m); 2.58 (2H,q, 7.4 Hz); 3.19 (6H,m); 3.70 (6H,m); 3.99 (4H,m); 6.92 (6H,m); 7.26 (3H,m); 11.70 (1H,bs).

EXAMPLE 5

5-Ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one (VIIIa, n = 2)



(a) 3-Phenoxypropionyl Hydrazide Hydrochloride.- Ethyl 3-phenoxypropionate (1481.0 g., 7.62 mole) obtained according to R. Hall, et al., J. Chem. Soc., 2035 (1949) is stirred in an ice bath during addition of 95% hydrazine (308.3 g., 9.14 mole). A precipitate forms and the mixture is allowed to stand at room temperature for 5 hr., then refrigerated for a 16 hr. period and filtered to provide 1128.0 g., of white solid (82.1% yield) of 3-phenoxypropionyl hydrazide. Preparation of the hydrochloride salt is carried out by dissolving 3-phenoxypropionyl hydrazide (2000.6 g., 11.1 mole) in 5 liters of methylene chloride. The solution is stirred and chilled in an ice bath as anhydrous hydrogen chloride is bubbled into the mixture to pH 3. Solid is collected, rinsed with methylene chloride and air dried to give 2100.0 g., (87.1% yield) of 3-phenoxypropionyl hydrazide hydrochloride, m.p. 145-156°C.

(b) 1-Propionyl-4-(2-phenoxyethyl)semicarbazide.- A mixture of 3-phenoxypropionyl hydrazide hydrochloride (938.9 g., 4.333 mole), 6.8 kg. ice-water and 3.4 liters toluene is stirred in

(33)

an ice bath as a solution of sodium nitrite (328.6 g., 4.763 mole) in 1.4 liters of water is added over a 10 min. period. The mixture is stirred for 0.5 hrs. at 2°C., Celite (Registered Trade Mark) added and the mixture filtered through a Celite bed. The filtrate layers are separated, and the aqueous layer extracted with two 400 ml. portions of toluene. Combined toluene extracts are dried over magnesium sulfate, filtered and the toluene solution of 3-phenoxypropionyl azide added over a 1.5 hr. period to a flask heated on a steam-bath under a nitrogen atmosphere with stirring. Following addition, decomposition of the azide to the phenoxyethyl isocyanate intermediate is completed by heating and stirring until gas evolution stops. The clear, yellow solution is cooled to 20°C. and propionyl hydrazide (381.8 g., 4.333 mole) obtained according to T. Rabini, et al., J. Org. Chem., 30, 2486 (1965) is added in one portion with stirring. Stirring is continued and the reaction mixture chilled to 10°C. and filtered affords 792.2 g., (72.8% yield) of 1-propionyl-4-(2-phenoxyethyl)-semicarbazide, m.p. 178-183°C.

(c) 5-Ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one.- A solution of potassium hydroxide (88.4 g., 1.576 mole) in 10 liters of water is stirred and heated to 95°C.; then 1-propionyl-4-(2-phenoxyethyl)-semicarbazide (396.1 g., 1.576 mole) added and the mixture stirred at 95-96°C. for a 40 min. period. Insolubles are collected and the filtrate stirred in an ice bath as 145 ml. (1.74 mole) of 37% hydrochloric acid is added. Stirring is continued with cooling to provide a white solid which is collected, rinsed with water and air dried to provide 233.5 g., (63.5% yield) of 5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one, m.p. 136-139°C.

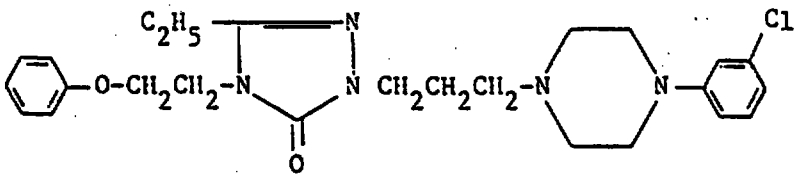
(34)

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01.

Found: C, 61.77; H, 6.50; N, 17.91.

EXAMPLE 6

2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]-propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxy ethyl)-3H-1,2,4-triazol-3-one



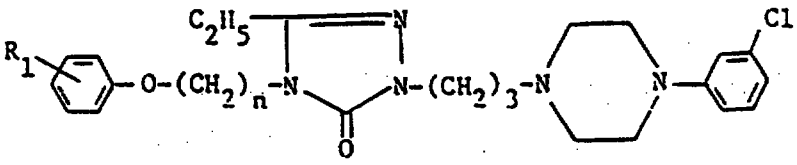
Reaction in Isopropanol with Sodium Hydroxide.- A mixture of 5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one (60.0 g., 0.257 mole), 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine hydrochloride (79.7 g., 0.257 mole), sodium hydroxide (26.7 g., 0.669 mole) and 400 ml. of isopropanol is stirred and heated at reflux for a period of 10 to 18 hrs. The mixture is acidified with 35 ml. (0.42 mole) of 37% hydrochloric acid and the solvent concentrated under reduced pressure. Residual material is stirred with 400 ml. of methylene chloride, filtered, and the filtrate concentrated under reduced pressure. Crystallization of the residue from 600 ml. of isopropanol affords 81.5 g. (62.5% yield) of product which is further crystallized from water and then isopropanol to provide 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride, m.p. 180-182.5°C.

Spectral (NMR, ^{13}C NMR, IR) and elemental analysis data are consistent and in accord with that obtained for the identical product of Example 2.

EXAMPLE 7

Additional Formula I Products

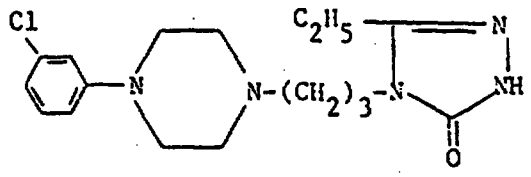
By substituting the enumerated phenoxyalkyl halide for phenoxyethyl bromide in Example 2, alkylation of 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5 ethyl-1H 1,2,4-triazol-3(2H)-one is carried out to provide the indicated compounds.



Compound		Phenoxyalkyl halide
R_1	n	
4-Cl	2	4-chlorophenoxyethyl chloride
3-Cl	2	3-chlorophenoxyethyl chloride
4-F	2	4-fluorophenoxyethyl bromide
4-F	3	4-fluorophenoxypropyl chloride
3-CH_3O	2	3-methoxyphenoxyethyl chloride
4-CH_3O	2	4-methoxyphenoxyethyl chloride

EXAMPLE 8

4-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (IIa)



(a) 1-(3-Chloropropyl)-4-(3-chlorphenyl)piperazine Hydrochloride.- A 50% sodium hydroxide solution (430.6 g., 5.333 mole) is added dropwise to a stirred solution of 1-(3-chlorophenyl)piperazine hydrochloride (502.0 g., 2.153 mole) and 1-bromo-3-chloropropane (339.0 g., 2.153 mole) in 435 ml. water and 535 ml. acetone while maintaining temperature of 0-10°C. Stirring is continued for a 16 hr. period at room temperature and the upper organic phase then separated and concentrated under reduced pressure. The remaining residual oil is taken up in 500 ml. acetone, filtered and the filtrate concentrated under reduced pressure to an oily residue which is dissolved in boiling dilute hydrochloric acid (1.67 liter water plus 280 ml. concentrated HCl, 3.36 mole). The oil which initially

separates from the cooled acid solution, solidifies on standing and is collected, rinsed with cold water and air dried. Crystallization of this material from water employing activated charcoal affords 438.4 g. (66%) of 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine hydrochloride, m.p. 196.5-198.5°C. The hydrochloride salt is converted to the free base with aqueous 10% sodium hydroxide and recovered by extracting with ether (dried over magnesium sulfate). Concentration of the etheral extract affords 1-(3-chloropropyl)-4-(3-chlorophenyl)-piperazine free base as an oily residue.

(b) Reaction in Xylene. Sodium hydroxide (4.2 g., 0.105 mole) in 20 ml. of water is added to 5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (11.96 g., 0.105 mole) obtained according to the procedure of J. Org. Chem., 41, 3233-3237 (1976) in 120 ml. of ethanol. Following addition, distillables are removed under reduced pressure, ethanol added to residual material and removed under reduced pressure and the process repeated until the sodium salt of 5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one is obtained as a dry solid.

The sodium salt is pulverized, suspended in 600 ml. of xylene and mixed with 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine free base (28.6 g., 0.105 mole). The resulting mixture is refluxed with stirring for 60 hrs. and the reaction mixture filtered and concentrated under reduced pressure. Residual material taken up in 40 ml. of ethanol and acidified with ethanolic hydrogen chloride provides, on standing, 8.7 g. of solid further purified by crystallization from ethanol to afford 6.3 g. (15.5% yield) of 4-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one hydrochloride, m.p. 213-215°C.

An analytical sample prepared in a similar manner melted at 210-212°C.

Anal. Calcd. for $C_{17}H_{24}ClN_5O \cdot HCl$: C, 52.85; H, 6.52; N, 18.13. Found: C, 53.03; H, 6.47; N, 18.16.

NMR (DMSO-d_6): 1.17 (3H, t, 7.3 Hz); 2.09 (2H, m); 2.57 (2H, q, 7.3 Hz); 3.19 (8H, m); 3.62 (4H, m); 6.92 (3H, m); 7.23 (1H, t, 7.7 Hz); 11.40 (1H, bs).

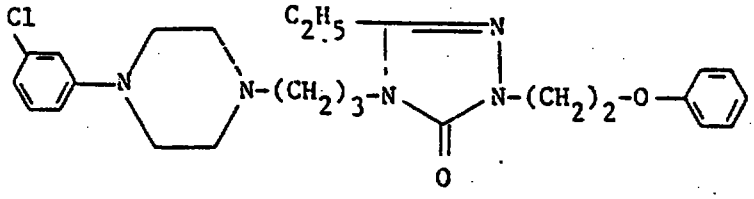
^{13}C NMR (ppm): 9.56, 18.36, 23.36, 37.43, 45.07, 50.51, 52.92, 113.98, 115.07, 118.91, 130.48, 133.87, 148.07, 150.90, 155.15.

(c) Reaction in Acetonitrile With Potassium Carbonate.- A mixture of 5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (11.3 g., 0.1 mole), 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine (27.32 g., 0.1 mole), pulverized potassium carbonate (27.64 g., 0.2 mole) and a trace of potassium iodide in 230 ml. of acetonitrile is refluxed for 18 hrs. and filtered. Concentration of the filtrate under reduced pressure and acidification of residual material in ethanol with ethanolic hydrogen chloride provides the hydrochloride salt purified by crystallization from ethanol to afford 11.0 g. (28.6% yield) of 4-[3-[4-(3-chlorphenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one hydrochloride, m.p. 209-211°C.

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EXAMPLE 9

4-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-2-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one



(a) Reaction in Xylene.- Sodium hydroxide (1.2 g., 0.03 mole) in 5-10 ml. of water is added to 4-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one hydrochloride (5.8 g., 0.015 mole) in 100 ml. of ethanol. After mixing, distillables are removed under reduced pressure and residual material repeatedly taken up in ethanol and concentrated until the dry sodium salt of 4-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one is obtained as a hard solid.

The sodium salt is pulverized, suspended in 100 ml. of xylene and mixed with phenoxyethyl bromide (3.02 g., 0.015 mole). The resulting mixture is refluxed with stirring for a 60-70 hr. period and the hot reaction mixture filtered and concentrated under reduced pressure to provide 7.46 g., of the crude free base as an oil. Purification of the free base is carried out chromatographically employing a silica column with ethanol/chloroform eluant. Free base, obtained from the chromatographic separation, is converted to the hydrochloride salt and crystallized from ethanol to afford 2.8 g. (37% yield) of analytically pure 4-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-5-ethyl-2,4-dihydro-2-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride, m.p. 182-184°C.

Anal. Calcd. for $C_{25}H_{32}ClN_5O_2 \cdot HCl$: C, 59.29; H, 6.57; N, 13.83. Found: C, 59.37; H, 6.74; N, 13.53.

NMR (DMSO-d_6): 1.18 (3H, t, 7.2 Hz); 2.15 (2H, m); 2.62 (2H, q, 7.2 Hz); 3.18 (6H, m); 3.68 (6H, m); 4.01 (2H, t, 6.0 Hz); 4.25 (2H, t, 6.0 Hz); 6.95 (6H, m): 7.28 (3H, m); 11.70 (1H, bs).

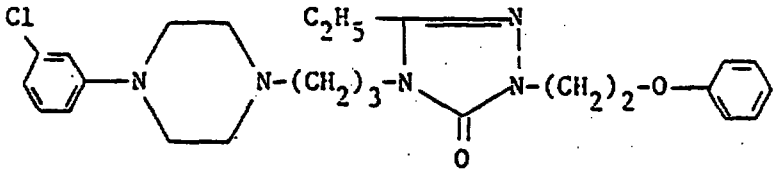
(b) Reaction in Acetonitrile With Potassium Carbonate.- A mixture of 4-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one hydrochloride (10.8 g., 0.028 mole), phenoxyethyl bromide (5.83 g., 0.028 mole), potassium carbonate (11.6 g., 0.084 mole) and a trace of potassium iodide in 100 ml. of acetonitrile is refluxed for a 66 hr. period. The hot reaction mixture is filtered, the filtrate concentrated under reduced pressure and residual material taken up in chloroform. The chloroform solution is washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to provide 13.2 g. of the free base product, 4-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-2-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one. The free base is converted to the hydrochloride salt in ethanol with ethanolic hydrogen chloride and crystallized from ethanol to afford a 71% yield of analytically pure 4-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-2-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride, m.p. 175-177°C.

Anal. Calcd. for $C_{25}H_{32}ClN_5O_2 \cdot HCl$: C, 59.29; H, 6.57; N, 13.83. Found: C, 59.04; H, 6.61; N, 13.98.

NMR (DMSO-d_6): 1.18 (3H, t, 7.2 Hz); 2.16 (2H, m); 2.62 (2H, q, 7.2 Hz); 3.18 (6H, m); 3.68 (6H, m); 4.01 (2H, t, 6.0 Hz); 4.25 (2H, t, 6.0 Hz); 6.95 (6H, m); 7.28 (3H, m); 11.70 (1H, bs).

EXAMPLE 10

4-[3-[4-(3-Chlorophenyl-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-2-(3-phenoxypropyl)-3H-1,2,4-triazol-3-one



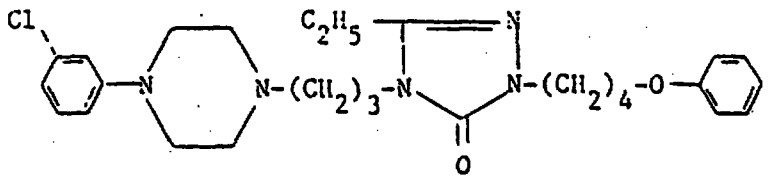
A mixture of 3-phenoxypropyl bromide (3.01 g., 0.014 mole), 4-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one hydrochloride (5.4 g., 0.014 mole), pulverized potassium carbonate (5.8 g., 0.042 mole) and a trace of potassium iodide in 50 ml. of acetonitrile is refluxed for a 20 hr. period. The hot reaction mixture is filtered, the filtrate concentrated under reduced pressure and residual material taken up in chloroform and filtered. Solvent is removed and further purification carried out chromatographically employing a silica gel column with ethanol/chloroform eluent. The chromatographically purified material is taken up in ether and acidified with ethanolic hydrogen chloride to provide a solid which is triturated with ethanol to provide 1.6 g. (20% yield) of 4-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-2-(3-phenoxypropyl)-3H-1,2,4-triazol-3-one dihydrochloride hydrate, m.p. 146-148°C.

Anal. Cacld. for $C_{26}H_{34}ClN_5O_2 \cdot 2HCl \cdot 0.75\ H_2O$: C, 54.75; H, 6.63; N, 12.28. Found: C, 55.03; H, 6.54; N, 12.49.

NMR (DMSO-d_6): 1.19 (3H, t, 7.3 Hz); 2.15 (4H, m); 2.62 (2H, q, 7.3 Hz); 3.20 (6H, m); 3.80 (8H, m); 4.01 (2H, t, 6.0 Hz); 6.96 (6H, m); 7.29 (3H, m); 7.78 (3H, bs); 11.80 (1H, bs).

EXAMPLE 11

4-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-2-(4-phenoxybutyl)-3H-1,2,4-triazol-3-one



A mixture of 4-phenoxybutyl chloride (2.29 g., 0.01 mole), 4-[3-[4-(3-chlorphenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one hydrochloride (3.86 g., 0.01 mole), pulverized potassium carbonate (4.15 g., 0.03 mole) and a trace of potassium iodide in 50 ml. of acetonitrile is refluxed for a 65 hr. period. The hot reaction mixture is filtered, the filtrate concentrated under reduced pressure and residual material taken up in ether and filtered. Solvent is removed and further purification carried out chromatographically employing a silica gel column with ethanol/chloroform eluent. The chromatographically purified material is taken up in ethanol and acidified with ethanol hydrogen chloride to provide 2.17 g. of 4-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4dihydro-2-(4-phenoxybutyl)-3H-1,2,4-triazol-3-one hydrochloride hyrate, m.p. 125-127°C.

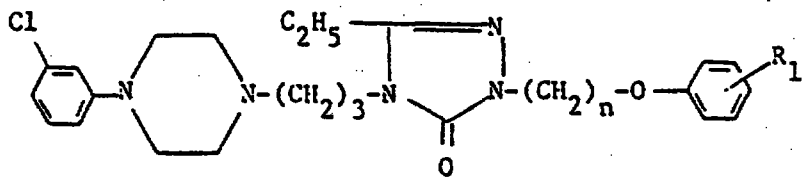
Anal. Calcd. for $C_{27}H_{36}ClN_5O_2 \cdot HCl \cdot 1/4\ H_2O$: C, 60.17; H, 7.02; N, 13.00. Found: C, 60.19; H, 7.11; N, 12.89.

NMR (DMSO-d_6): 1.18 (3H, t; 7.4 Hz); 1.75 (4H, m); 2.16 (2H, m); 2.61 (2H, q, 7.4 Hz); 3.18 (6H, m); 3.80 (6H, m); 3.96 (4H, m); 6.92 (6H, m); 7.25 (3H, m); 11.75 (1H, bs).

EXAMPLE 12

Additional Products

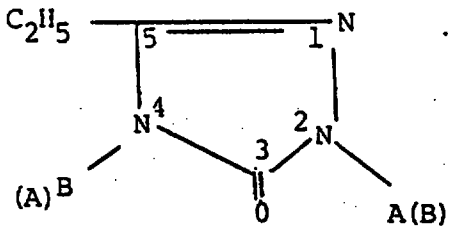
By substituting the enumerated phenoxyalkyl halide for phenoxyethyl bromide in Example 9, alkylation of 4-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl-5-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one is carried out to provide the indicated compounds.



Compound		Phenoxyalkyl halide
R_1	n	
4-Cl	2	4-chlorophenoxyethyl chloride
3-Cl	2	3-chlorophenoxyethyl chloride
4-F	2	4-fluorophenoxyethyl bromide
4-F	3	4-fluorophenoxypropyl chloride
$3-CH_3O$	2	3-methoxyphenoxyethyl chloride
$4-CH_3O$	2	4-methoxyphenoxyethyl chloride

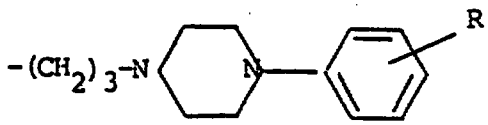
CLAIMS :

1. A compound of Formula I

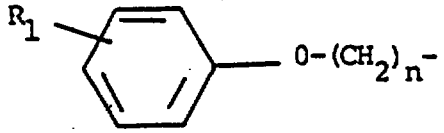


(I)

wherein A is a radical of the formula



and B is a radical of the formula



and, wherein R_1 is hydrogen, halogen or alkoxy of 1-4 carbon atoms, n is 2-4, R is halogen or a pharmaceutically acceptable acid addition salt thereof.

2. The compound of Claim 1 wherein R_1 is hydrogen, n is 2 and R is meta-chloro.

3. The compound of Claim 1 or 2 which is 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one.

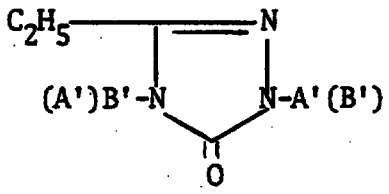
4. The compound of Claim 1 or 2 which is 2-[3-[4-(chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4,-dihydro-4-(2-phenoxyethyl)-3H-1,2,4,-triazol-3-one hydrochloride.

5. The compound of claim 1 or 2 which is 4-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl] -5-ethyl-2,4-dihydro-2-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one.

6. The compound of claim 1 or 2 which is 4-[3-[4-(3-chlorophenyl)-1-piperazinyl] propyl] -5-ethyl-2,4-dihydro-2-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride.

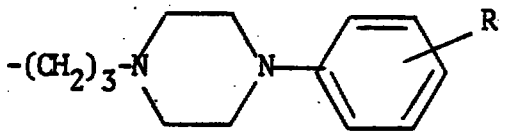
7. The pharmaceutical composition comprising an antidepressant amount of a compound of any of claims 1-6 or a pharmaceutically acceptable acid addition salt thereof and a pharmaceutically acceptable carrier.

8. A process for the preparation of a compound of any of claims 1-6 which comprises alkylating a compound of the formula



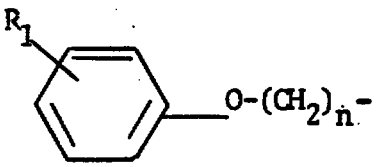
(X)

wherein A' is hydrogen or a 1-(halophenyl)-4-(3-halopropyl)piperazine radical



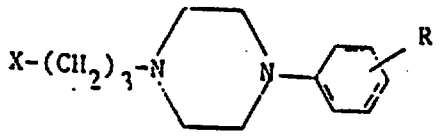
and

B' is hydrogen or the phenoxyalkyl radical



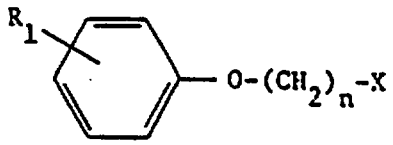
* C L M S *

in which "R_1" is as defined above, "n" is the integer 2 to 4 and one of "A" or "B" must be hydrogen with an alkylating agent of the formula



(IX)

wherein R is halogen and X is halogen or a suitable leaving group or an alkylating agent of the formula



(VII)

wherein R^1 and n are defined above and X is halogen or a suitable leaving group.

9. A pharmaceutical compound as defined in Claim 1 for use in a method of treatment of the human or animal body.

10. A compound according to claim 9 for use as an anti-depressant.

11. A compound according to Claim 1 substantially as hereinbefore specifically described in ———— examples for the use hereinbefore specifically described.

12. A compound as defined in Claim 1 substantially as hereinbefore specifically described in examples.

13. A pharmaceutical composition according to claim 7 substantially as hereinbefore specifically described.

14. A process according to Claim 8 for making a compound as defined in Claim 1 substantially as hereinbefore specifically described in examples.

15. A compound when produced by a process as claimed in either

* C L M S *

of Claims 8 and 14.