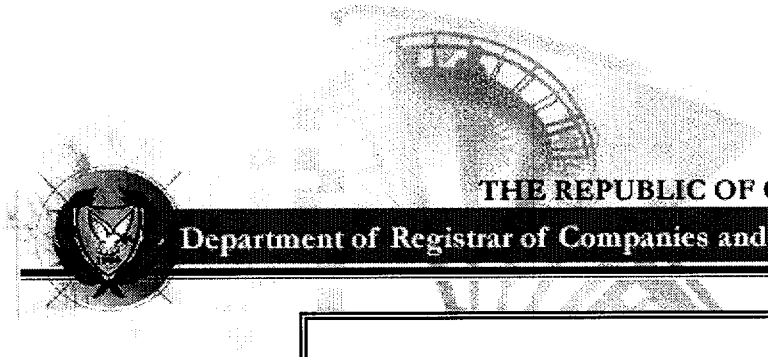

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

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ΓΡΑΦΕΙΟΥ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

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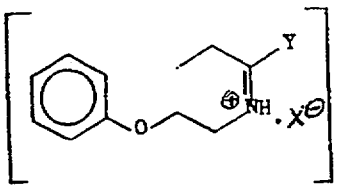
(54) Intermediates in process for production of 1,2,4-triazolones

(57) In a novel process for the preparation of 5-ethyl-4-(2-phenoxyethyl)-1,2,4-triazolone (used in the synthesis of antidepressant 1,2,4-triazolones typified by 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2*H*-1,2,4-triazol-3(4*H*)-one, also known as nefazodone), novel intermediate acid addition salts of formula



III

and processes for their preparation are disclosed.

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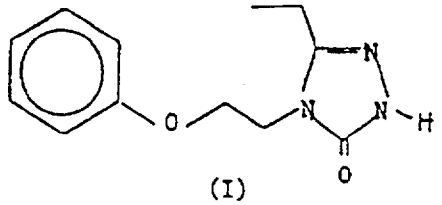
SPECIFICATION

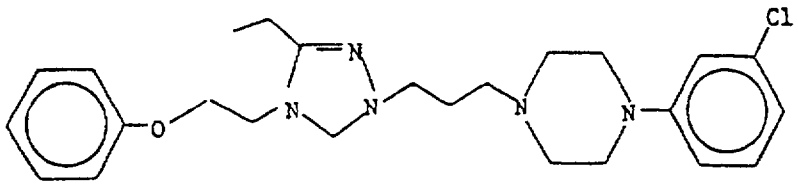
Intermediates in process for production of 1,2,4-triazolones

Reference is made to co-pending U.K. Patent Application No. 8430275 which discloses and claims an improved, more economical process for the synthesis of a valuable chemical intermediate (I)



(I)

used in the manufacture of the antidepressant agent 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2*H*-1,2,4-triazol-3(4*H*)-one which is also known as nefazodone.

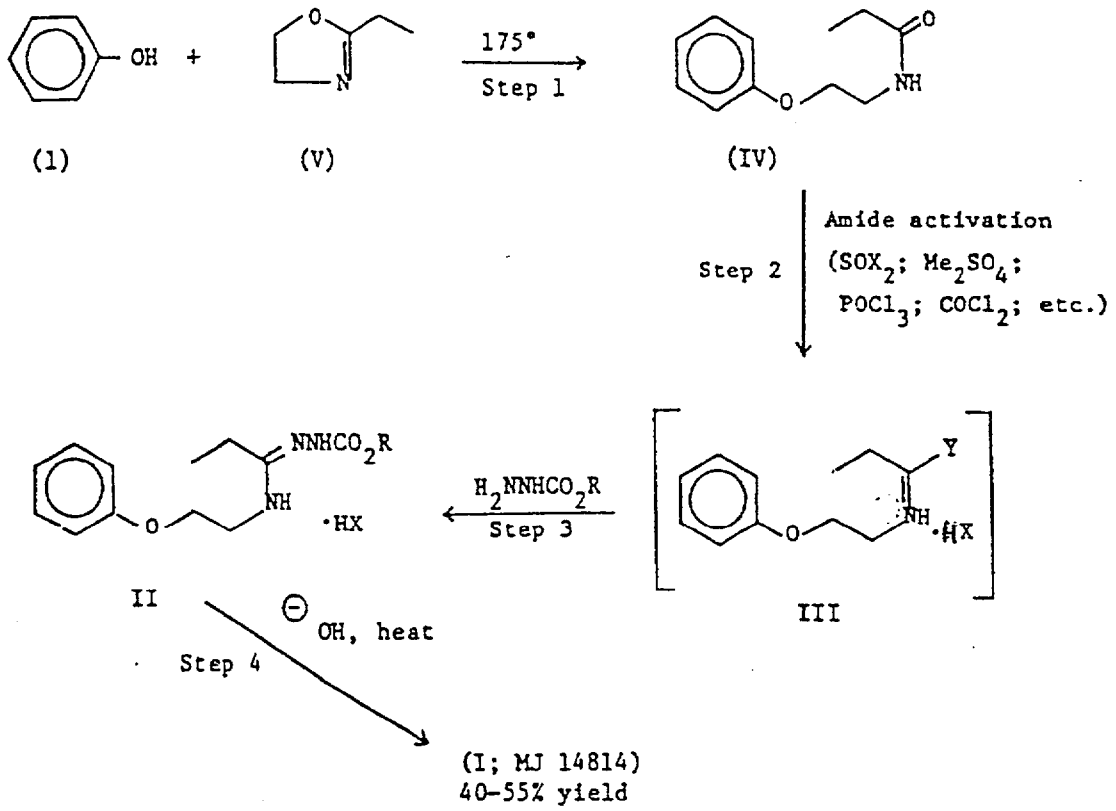


nefazodone

The above compound of formula I is also known as MJ 14814.

The improved process disclosed in the above co-pending application offers advantages in economies of both material and labor costs by virtue of being shorter in length, involving fewer intermediate isolations, and providing a higher yield of product.

The following flow chart, Scheme 5, illustrates the preparation of MJ 14814 from readily available starting materials utilizing the process of GB 8430275.



In Scheme 5, R is C_{1-4} alkyl; X is Cl, Br, or SO_4; Y is Cl, Br, or OR; and amide activation is formation of a reactive imidoyl halide or ester by treatment of the amide with a suitable activating reagent such as $SOCl_2$, $SOBr_2$, $POCl_3$, dimethyl sulfate, phosgene, etc.

Step 1 of the scheme outlined above involves the reaction of phenol (1) and 2-ethyl-2-oxazoline (V) to give the intermediate compound N-(2-phenoxyethyl)propionamide (IV). The starting materials for step 1 are commercially available. Step 2, activation of the amide (IV), is accomplished by treatment of IV with an amide-activating reagent such as thionyl chloride, thionyl bromide, phosphorus oxychloride, phosgene, dimethyl sulfate, and the like, to give an imidoyl halide or ester intermediate (III). The preferred agents are phosgene or phosphorus oxychloride. Intermediate III need not be isolated but can be allowed to react with an alkyl carbazate of formula H_2NNHCO_2R, R = methyl is preferred, in step 3 to give the novel triazolone precursor (II). In step 4 the hydrazinecarboxylate acid addition salt (II) is converted to its base form and cyclized to the desired triazolone product (I) by heating.

This four-step improved process involves isolation of only two intermediate products (IV and II) in addition to the target

The synthesis of MJ 14814 as represented in the above process is preferably carried out as a series of four steps going from the simplest starting materials (phenol, 2-ethyloxazoline) to MJ 14814. The steps comprising the process are as follows:

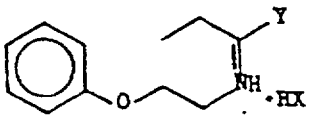
(1) Adding 2-ethyl-2-oxazoline to hot (150°) phenol and maintaining heating at about 175° for 16 additional hours. The oil is then quenched in water to give N-(2-phenoxyethyl)propionamide (IV) in approximately 90% yield.

(2) Adding phosgene or phosphorus oxychloride to a solution of IV containing a catalytic amount of imidazole in methylene chloride to give a solution of the intermediate imidoyl chloride hydrochloride (III).

(3) Treating the solution of III with a solution of an alkyl carbazate to give alkyl [1-[(2-phenoxyethyl)amino]propylidene]-hydrazine carboxylate hydrochloride (II) is about 75% yield.

(4) The free base form of II, resulting from the treatment of II with a basifying agent, is heated in solution for several hours to yield I in about 75%.

The present invention is directed to the intermediates of formula III and in one aspect provides an imidoyl halide or ester of formula

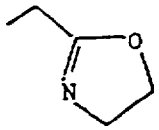


III

wherein Y is a halogen or alkoxy moiety and X is an anion.

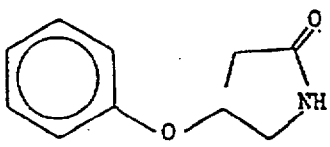
In another aspect the invention provides a process for the production of a compound of formula III wherein Y is a halogen or alkoxy moiety and X is an anion comprising:

a) reacting phenol with 2-ethyl-2-oxazoline (V)



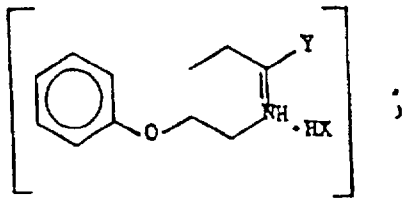
(V)

to give N-(2-phenoxyethyl)propionamide (IV)



(IV)

b) activating the amide functional group of compound IV by reacting compound IV with an amide-activating agent so as to produce an imidoyl halide or ester intermediate of formula III;



III

said amide activating agent containing precursors of X and Y wherein Y is a halogen or alkoxy moiety and wherein X is an anion which results from the reaction between said amide-activating agent and compound IV.

Preferably said amide-activating agent is thionyl chloride, thionyl bromide, phosphorous oxychloride, phosgene or dimethyl sulphate.

The process involving the intermediates of this invention and their synthesis is illustrated in greater detail by the following non-limiting examples. In examples which follow, used to illustrate the fore-going processes, temperatures are expressed, as in the foregoing in degrees centigrade (°). Melting points are uncorrected. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed as parts per million (ppm) versues tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the H NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Abbreviations employed are DMSO-d_6 (deuterodimethylsulfoxide), $CDCl_3$ (deuterochloroform), and are otherwise conventional. The infrared (IR) spectral descriptions include only absorption wave numbers (cm^{-1}) having functional group identification value. The IR determinations were employed using potassium bromide (KBr) as diluent. The elemental analyses are reported as percent by weight.

Example 1

Methyl carbazate

An alternate name for this commercially available chemical is methyl hydrazinocarboxylate. Methyl carbazate may also be synthesized by adding 85% hydrazine hydrate (58.5 g, 1.00 mole) with stirring to dimethyl carbonate (90.0 g, 1.00 mole) over a 10 min period. The mixture quickly warmed to 64° and became clear. The solution was stirred for another 15 min and the volatile materials were stripped *in vacuo* at 70°. Upon cooling, the residue solidified. It was collected on a filter and after drying in air gave 69.3 g (76.9%) of white solid, m.p. 69.5-71.5°.

Example 2

N-(2-Phenoxyethyl)propionamide (IV)

Phenol (13.1 moles) was heated to 150° and stirred under N_2 as 2-ethyl-2-oxazoline (12.2 moles) was added over 1 hr. The mixture was heated to 175 ± 3°. After heating 16 hr the oil was cooled to about 140°, and then it was poured into water (12 L) with vigorous stirring. The mixture was stirred and cooled, and at about 25° the mixture was seeded with crystalline amide product. The material solidified and the supernatant was decanted. The residual solid was stirred with 17 L of hot (85°) water. The mixture was cooled to 25°, seeded with the amide product, and the mixture refrigerated. The resulting granular solid was collected on a filter, rinsed with several portions of water and left to air dry. This gave a 92% yield of material, m.p. 61.5-64°.

Example 3

A. *Methyl [1-[(2-Phenoxyethyl]amino]propylidene hydrazinecarboxylate hydrochloride (II)*

Phosgene (57.4 g, 0.58 mole) was added to a solution of N-(2-phenoxyethyl)propionamide (IV, 112.0 g, 0.58 mole) and imidazole (0.4 g, 0.006 mole) in 450 mL methylene chloride over 1 hr employing cooling so that the temperature did not exceed 25°. The reaction solution was then stirred at 25° for an additional 2.5 hr. A solution of methyl carbazate (52.5 g, 0.58 mole) in 500 mL methylene chloride was stirred over 25 g of a molecular sieve for 15 min and then the solution was filtered. The filtrate was added under N_2 over a 0.5 hr period to the amide/phosgene solution while employing cooling 15-20°. A voluminous precipitate formed and the mixture was left to stir at 25° under N_2. After stirring for a total of 16 hrs, the mixture was filtered to isolate a solid. The solid was stirred in 750 mL methylene chloride for 15 min, refiltered, and then dried *in vacuo* at 65° for 2 hrs to give 135 g (77%) while solid, m.p. 150-154°. Recrystallization of the product from isopropanol gives analytically pure material, m.p. 157-159°.

Anal. Calcd. for $C_{13}H_{19}N_3O_3 \cdot HCl$: C, 51.74; H, 6.68; N, 13.92; Cl, 11.75. Found: C, 51.73; H, 6.76; N, 13.94; Cl, 11.78.

NMR (DMSO-d_6): 1.15 (3,t[7.5 Hz]); 1.28 (3, t[7.5 Hz]); 2.74 (2,m); 3.66 (3,s); 3.70 (3,s); 3.81 (2,m); 4.19 (2,m); 6.98 (3,m); 7.31 (2,m); 9.67 (3,bt[6.8 Hz]); 10.04 (3,bs); 10.40 (3,bs); 10.90 (3,bs); 11.72 (3,bs).

IR (KBr); 695, 755, 1250, 1270, 1500, 1585, 1600, 1670, 1745, and 2900 cm^{-1}.

By appropriate modification of the above procedure (A), thionyl chloride, thionyl bromide, dimethyl sulfate

or other amide-activating agents may be employed in place of phosgene. A slightly different procedure (B) may also be used.

B. *Methyl [1-[(2-Phenoxyethyl]amino]propylidene hydrazinecarboxylate (II Base Form)*

Phosphorus oxychloride (53.0 g, 0.346 mole) was slowly added to a solution of N-(2-phenoxyethyl)propionamide (IV, 100.0 g, 0.518 mole) in 200 mL ethylene chloride while being stirred under nitrogen. This solution was stirred for 4 hrs at which time a solution (dried over moecular sieve 4A) of methyl carbazate (46.4 g, 0.518 mole) in 600 mL methylene chloride was added to the stirring solution over a 0.5 hr period. The resulting mixture was stirred and heated at gentle reflux under nitrogen for 18 hr. The mixture was then stirred with 1.0 L ice-water. The layers were separated and the aqueous layers extracted with an additional 200 mL methylene chloride. The aqueous layer was made basic (pH 12) with aqueous sodium hydroxide. This resulted in precipitation of the free base form of II which was collected by filtration, rinsed with water and dried in air to give 65.8 g of product, m.p. 97-99°.

Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 59.02; H, 7.24; N, 15.92.

When this free base form of II is employed for the conversion to I, the preliminary basification step outlined in Example 4 (which follows) is skipped. The base form of II is cyclized directly by gently refluxing in xylene according to the procedure of Example 4.

Example 4

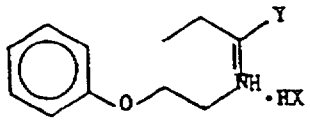
5-ethyl-4-(2-phenoxyethyl)-2H-1,2,4-triazol-3(4H)-one (I)

Methyl [1-[(2-phenoxyethyl)amino]propylidene]hydrazine carboxylate hydrochloride (II, 655.3 g, 2.17 mole) was stirred vigorously with 4.0 L methylene chloride, 2.4 L water and 179.4 g 50% NaOH (2.24 moles). The layers were separated and the organic layer was dried (K_2CO_3) and concentrated *in vacuo*. The residue was stirred in 1.2 L xylene at gentle reflux for 2.5 hrs and then the solution was refrigerated. The solid was collected on a filter, rinsed with toluene and left to air dry. The white crystalline solid weighed 89.5 g (76.9%), m.p. 134.5-138°.

Additional purification may be accomplished in the following manner. A portion of I (171.2 g, 0.73 mole) was dissolved in a boiling solution of 41.0 g (0.73 mole) KOH in 3.0 L water. The solution was treated with Celite (Registered Trade Mark) filter-aid and activated charcoal and filtered. The filtrate was stirred in an ice bath, and 37% HCl (61.0 mL, 0.73 mole) was added. The solid was collected on a filter, rinsed with water and air dried to give 166.0 g (97% recovery) of fine white crystalline product, m.p. 137.5-138°.

CLAIMS

1. An imidoyl halide or ester of formula



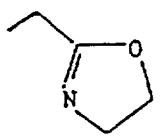
III

wherein Y is a halogen or alkoxy moiety and X is an anion.

2. A compound of formula III substantially as hereinbefore described in Example 3.

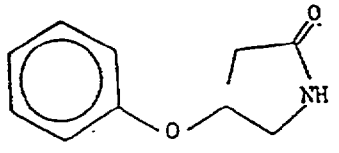
3. A method for the production of a compound according to claim 1 comprising :

a) reacting phenol with 2-ethyl-2-oxazoline (V)



(V)

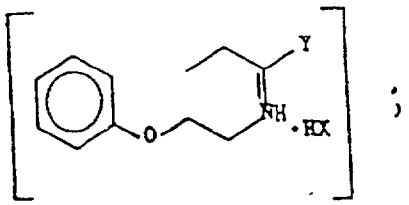
to give N-(2-phenoxyethyl)propionamide (IV)



;

(IV)

b) activating the amide functional group of compound IV by reacting compound IV with an amide-activating agent so as to produce an imidoyl halide or ester intermediate of formula III;



III

said amide activating agent containing precursors of X and Y wherein Y is a halogen or alkoxy moiety and wherein X is an anion which results from the reaction between said amide-activating agent and compound IV.

4. A method as claimed in claim 3 wherein said amide-activating agent is thionyl chloride, thionyl bromide, phosphorous oxychloride, phosgene or dimethyl sulphate.

5. A method for the production of a compound according to claim 4 substantially as hereinbefore described in Example 3.

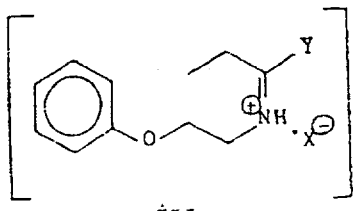
6. A compound of formula III when produced by a method according to either or claims 3 or 4.

Amendments to the claims have been filed, and have the following effect:-

(a) Claims 1 and 3 above have been deleted or textually amended.

(b) New or textually amended claims have been filed as follows:-

1. An imidoyl halide or ester of formula

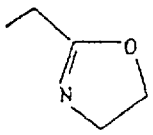


III

wherein Y is a halogen or alkoxy moiety and X is an anion.

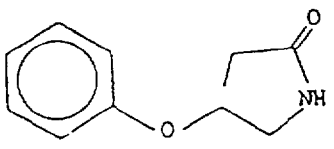
3. A method for the production of a compound according to claim 1 comprising:

a) reacting phenol with 2-ethyl-2-oxazoline (V)



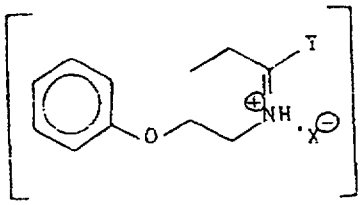
(V)

to give N-(2-phenoxyethyl)propionamide (IV)



(IV)

b) activating the amide functional group of compound IV by reacting compound IV with an amide-activating agent so as to produce an imidoyl halide or ester intermediate of formula III;



III

said amide activating agent containing precursors of X and Y wherein Y is a halogen or alkoxy moiety and wherein X is an anion which results from the reaction between said amide-activating agent and compound IV.

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