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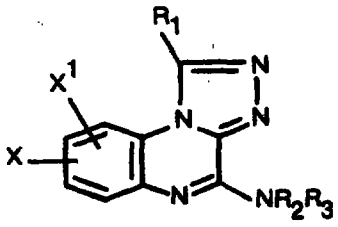
Description

This invention relates to a series of novel [1,2,4]triazolo[4,3-a]quinoxaline-4-amine derivatives and their pharmaceutically acceptable acid addition salts which are useful as antidepressant and anti-fatique agents.

An intensive search has been undertaken for agents which are effective in reducing the symptoms of depression and fatigue in mammals.

U.S. Patent No. 3,839,569 and West German Patent No. 2,249,350 respectively disclose the use of *s*-triazolo[4,3-a]quinolines and 1H-imidazo[4,5-b]quinoxalines as agricultural fungicides. U.S. Patent No. 4,008,322 discloses the use of a series of triazolo[4,3-a]quinoxaline derivatives for control of rice blast caused by the phytopathogen *Piricularia oryzae.*

The present invention relates to novel [1,2,4]triazolo[4,3-a]quinoxaline-4-amine derivatives useful as antidepressant and anti-fatigue agents. Specifically the compounds of the present invention are of the formula:



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein

X and X^1 are each selected from the group consisting of hydrogen, fluorine, chlorine, bromine and methoxy;

R_1 is selected from the group consisting of hydrogen, lower alkyl, lower perfluoroalkyl and phenyl; and

R_2 and R_3 are each selected from the group consisting of hydrogen, lower alkyl, phenylalkyl having up to three carbon atoms in the alkyl moiety and alkanoyl having from two to five carbon atoms, provided that at least one of R_2 and R_3 is always other than hydrogen where X and X^1 are each hydrogen and R_1 is hydrogen or methyl; or R_2 and R_3, when taken together, complete a piperazino ring.

For purposes of the present specification and claims, by lower alkyl is meant alkyl having 1 to 4 carbon atoms and by lower perfluoroalkyl is meant perfluoroalkyl having from 1 to 4 carbon atoms like trifluoromethyl and pentafluoroethyl, etc.

One group of compounds of interest are those wherein X and X^1 are each hydrogen, R_1 is hydrogen, and R_2 and R_3 are each lower alkyl. Preferred compounds include those wherein R_2 and R_3 are both ethyl.

Another group of compounds of the present invention are those wherein X and X^1 are each hydrogen, R_1 is ethyl and R_3 is lower alkyl. Preferred compounds are those wherein R_2 is hydrogen and R_3 is ethyl.

Still another group of compounds of the present invention are those wherein X and X^1 are each hydrogen, R_1 is lower alkyl and R_3 is acetyl. Preferred compounds include those wherein R_1 is ethyl and R_2 is hydrogen, ethyl or acetyl.

A further group of compounds of interest of the present invention are those wherein at least one of X and X^1 is fluorine, R_1 is hydrogen or trifluoromethyl, R_2 is hydrogen and R_3 is hydrogen, lower alkyl or alkanoyl having from two to five carbon atoms; or, alternatively, wherein at least one of X and X^1 is chlorine, R_1 is lower alkyl or trifluoromethyl, R_2 is hydrogen and R_3 is hydrogen, lower alkyl or alkanoyl having from two to five carbon atoms.

Also embraced by the present invention are pharmaceutical compositions comprising an antidepressant, antifatigue effective amount of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carier or diluent. Preferred pharmaceutical compositions are those containing the preferred compound of Formula I as described hereinabove.

The present invention also comprises the present compounds of Formula I for use in treating depression and fatigue in a mammal in need of such treatment, which comprises administering to said mammal an antidepressant/antifatigue effective amount if a compound of formula I or a pharmaceutically acceptable acid addition salt thereof. Preferred compounds for use in this method of treatment are the preferred compounds of formula I as described hereinabove.

The majority of the novel compounds of formula I may be prepared by the reaction sequence shown in reaction scheme I. The numbering of the phenyl and the two heterocyclic rings in scheme I is that employed throughout the specification.

In scheme I, a compound of formula IV, a quinoxaline derivative wherein X and X^1 are each hydrogen, fluorine, chlorine, bromine or methoxy, with the proviso that X is always hydrogen when said quinoxaline derivative is monosubstituted in the benzene ring, is treated with an excess molar amount of hydrazine hydrate in a polar, reaction-inert organic solvent such as an alkanol having from 1 to 3 carbons, preferably ethanol, at room temperature for a period of about 18-24 hours to form an intermediate compound of formula III.

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The intermediate compound of formula III may then be subsequently converted to the corresponding intermediate of formula IIA, wherein R_1 is other than lower perfluoroalkyl, by treatment with an appropriate alkyl orthoalkanoate or alkyl orthobenzoate, as the case may be, at a temperature between about 80° and 120°C. for about 1 to 24 hours. In the resulting compound of formula IIA, R_1 (as hydrogen or alkyl) is determined by the particular orthoalkanoate employed in the synthesis. Thus, for example, when triethyl orthoformate is used, R_1 is hydrogen, when triethyl orthopropionate is used, R_1 is ethyl and when triethyl orthoisobutyrate is used, R_1 is isopropyl.

The intermediate compound of formula III may also be converted to the corresponding intermediate of formula IIA wherein R_1 is lower perfluoroalkyl by treatment with an excess molar amount of an appropriate perfluoroalkanoic acid, such as trifluoroacetic acid or pentafluoropropionic acid, etc., as the case may be, in a conventional manner to yield the corresponding 4-hydroxy-1-perfluoroalkyl-[1,2,4]triazolo[4,3-a]-quinoxaline, followed by treatment of the latter type compound with phosphorus oxychloride in the presence of a tertiary amine, such as triethylamine, at elevated temperatures to yield the corresponding 4-chloro compound.

Intermediate IIA (wherein R_1 is hydrogen, lower alkyl, lower perfluoroalkyl or phenyl) is then converted to a [1,2,4]triazolo[4,3-a]quinoxaline-3-amine derivative of formula IA, wherein R_2 and R_3 are each as previously defined except that they are other than alkanoyl, by treatment with an excess molar amount of an amine of the formula HNR_2R_3 in a reaction-inert organic solvent, preferably N,N-dimethylformamide, at a temperature between about 0° and 60°C. for about 2 to 24 hours. For example, the preferred compounds of formula IA in which R_2 and R_3 are both ethyl are prepared by treating the appropriate compound of formula IIA with diethylamine in N,N-dimethylformamide at room temperature for 2—3 hours. Likewise, preferred compounds of formula IA wherein R_2 is hydrogen and R_3 is ethyl are prepared by treating a compound of formula IIA with monoethylamine in N,N-dimethylformamide at room temperature for 4 to 5 hours.

[1,2,4]Triazolo[4,3-a]quinoxaline-4-amine derivatives of the formula IA wherein at least one of R_2 and R_3 is alkanoyl having from two to five carbon atoms are prepared from the corresponding compounds of formula IA where at least one of R_2 and R_3 is hydrogen by contacting the latter with the appropriate alkanoic acid anhydride under substantially anhydrous conditions. This reaction can be carried out in the presence of an organic base, such as a tertiary amine, as catalyst (although this is not absolutely necessary) at a temperature ranging from about 20°C. up to about 140°C. for a period of about one-half to about 24 hours. The molar ratio of acid anhydride to the 4-amino starting material should be at least about 1:1 and preferably from about 4:1 to about 25:1, while the amount of tertiary amine employed is normally about 25 to 150% by weight of the aforesaid acylating agent (the tertiary amine may be used as the reaction solvent by merely employing an excess of same). Although it is quite possible and even, in some instances, highly desirable to carry out the reaction in the absence of a solvent, there may be times when the use of a suitable reaction-inert organic solvent is clearly indicated. Suitable organic solvents for use in this connection include neutral, reaction-inert anhydrous organic solvents, such as acetone, methyl ethyl ketone, benzene, toluene, xylene, dioxane, tetrahydrofuran, methylene chloride, chloroform, ethylene dichloride, tetrachloroethane, methyl acetate, ethyl acetate, isopropyl acetate, methyl propionate, ethyl propionate, diethyl ether, diisopropyl ether, di-n-propyl ether and the like. However, as previously indicated, the reaction is ordinarily conducted in the absence of such a solvent by merely employing an excess of acid anhydride. Similarly, an excess of the tertiary amine reagent may also serve as a solvent. Preferred tertiary amines for use as solvents and/or catalytic reagents in this reaction include triethylamine, dimethylaniline, pyridine, picoline, lutidine, collidine and quinoline.

The starting materials of formula IV wherein X and X^1 are each hydrogen are well known in the art. Compounds of formula IV wherein X^1 is methoxy may be prepared by the method of G. W. H. Cheeseman [J. Chem. Soc., p. 1170 (1962)] wherein 4-methoxy-*o*-phenylenediamine hydrochloride is treated with at least an equimolar amount of diethyl oxalate and diethylaminé under an atmosphere of inert gas, preferably nitrogen, at reflux temperature for about 2 to 3 hours, followed by treatment with phosphorus oxychloride in a tertiary amine, preferably dimethylaniline, at reflux temperatures for 1—2 hours.

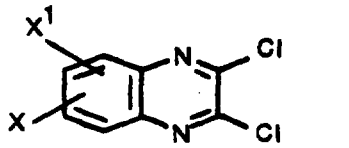
In reaction scheme II, a quinoxaline derivative of the formula IV, wherein X is fluorine, chlorine, bromine or methoxy and X^1 is hydrogen, is treated with sodium methoxide in an alcoholic solvent medium at slightly elevated temperatures (e.g., 40—60°C.) for a period of approximately 6—18 hours to form the corresponding 2-chloro-3-methoxyquinoxaline derivative of formula V, which is then treated with hydrazine hydrate in the same manner as before to yield the corresponding 2-hydrazino-3-methoxy-quinoxaline derivative of formula VI. The latter intermediate (VI) is then subsequently converted to the desired 7-substituted 4-methoxy[1,2,4]triazolo[4,3-a]quinoxaline derivative of formula VII by use of an appropriate ortho ester, or with perfluoroalkanoic acid, in the same manner as previously described, and the latter compound is then successively converted to the corresponding 4-hydroxy (see formula VIII) and 4-chloro compounds by conventional procedure to yield a compound of structural formula IIB wherein X is as hereinbefore defined above (i.e., other than hydrogen) and X^1 is hydrogen. This intermediate of formula IIB then leads to the corresponding novel final products of formula IB, wherein R^1, R^2 and R^3 are all as previously defined and X and X^1 are as above, by merely employing the reaction procedures previously described in connection with the discussion of the last stages of over-all scheme I.

The pharmaceutically acceptable acid addition salts of the novel compounds of formula I are also

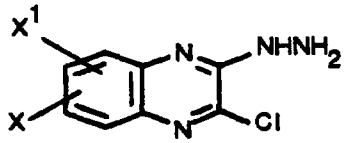
embraced by the present invention. These salts may be readily prepared by contacting the free base with an appropriate mineral or organic acid in either aqueous solution or in a suitable organic solvent. The solid salt may then be obtained by precipitation or by evaporation of the solvent. The pharmaceutically acceptable acid addition salts of this invention include, but are not limited to, the hydrochloride, sulfate, bisulfate, mesylate, tosylate, nitrate, phosphate, acetate, lactate, maleate, furmarate, citrate, tartrate, succinate, gluconate and the like. Mesylate salts are preferred. If desired, the compounds of formula I as the free base may be formed from the acid addition salts thereof by treatment with an appropriate base, followed by extraction of the free base with a suitable organic solvent.

The compounds of formula I and the pharmaceutically acceptable acid addition salts thereof have activity as anti-depressant and anti-fatigue agents and accordingly, are of therapeutic value in the treatment of symptoms associated with depression and fatigue. The compounds may be administered to a subject in need of treatment by a variety of conventional routes of administration including orally, and parenterally. Preferably, the compounds are administered orally. In general, these compounds will be administered orally at one or more doses between about 0.1 to 100 mg./kg. body weight of the subject to be treated per day, preferably from about 0.5 to 10 mg./k. per day. If parenteral or intravenous administration is desired, then these compounds can be given at doses between about 0.1 to 10 mg./kg. body weight of the subject to be treated per day. However, some variation in dosage will necessarily occur depending upon the condition of the subject being treated and the particular compound employed.

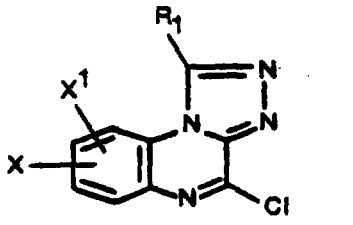
REACTION SCHEME I



IV

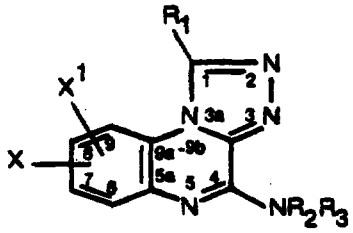


III



IIA

(Excludes X^1=H; X≠H)

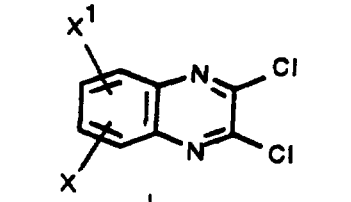


IA

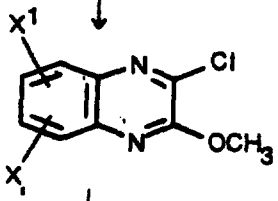
(Excludes X^1=H; X≠H)

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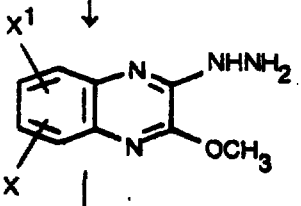
REACTION SCHEME II



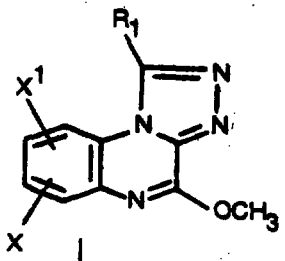
IV



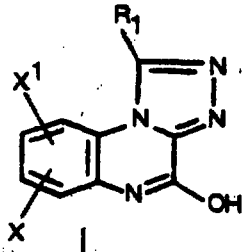
V



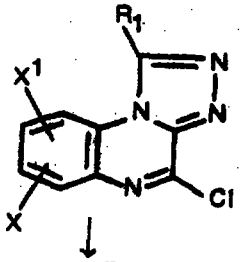
VI



VII

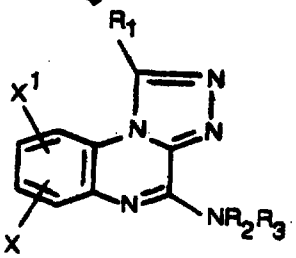


VIII



IIB

(X^1=H; X≠H)



IB

(X^1=H; X≠H)

(16)

The compounds may be administered alone or in combination with pharmaceutically acceptable carriers or diluents, in either single or multiple doses. Suitable pharmaceutical carriers include inert diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining the novel compounds of Formula I or salts thereof and pharmaceutically acceptable carriers are readily administered in a variety of dosage forms such as tablets, powders, capsules, lozenges, syrups and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for oral administration, tablets containing various excipients, such as sodium citrate, may be employed, together with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia.

The activity of the compounds of the present invention as antidepressant and anti-fatigue agents is determined by various standard pharmacological tests, including, for example, Porsolt's screening model of "learned helplessness", i.e., immobility induced by forced swimming in rats [R. D. Porsolt et al., European J. Pharmacol., *47*, 379 (1978)]. Pharmaceutical agents of this type which are therapeutically effective in humans are known to reduce immobility induced by forced swimming in this model.

The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the specific details of these examples. All temperatures are in degrees centigrade.

Preparation A

4-Chloro-7-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 2-chloro-6-fluoro-3-methoxyquinoxaline

In a flame-dried reaction flask containing a slurry of 52 g. (0.24 mole) of 2,3-dichloro-6-fluoroquinoxaline in 500 ml. of methanol under a dry nitrogen atmosphere, there was added slowly in a dropwise manner at 50°C. a solution consisting of 6.6 g. (0.29 mole) of sodium dissolved in 650 ml. of methanol. The resulting reaction mixture was then heated at 50°C. overnight (i.e., for a period of approximately 16 hours) and the clear solution so obtained was allowed to cool to room temperature (~20°C.). The reaction mixture was then concentrated *in vacuo*, and the residual material subsequently dissolved in chloroform, washed with water and dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was ultimately obtained a liquid residue that was subsequently chromatographed on a 1000 ml. silica gel column, followed by elution with toluene. The combined fractions containing only product then gave 48.3 g. (95%) of pure 2-chloro-6-fluoro-3-methoxyquinoxaline, m.p. 93—95°C. Mass Spectrum: m/e 212(P)) m/e 214 (P + 2).

b) Preparation of 6-fluoro-2-hydrazino-3-methoxyquinoxaline

To a solution consisting of 47 g. (0.22 mole) of 2-chloro-6-fluoro-3-methoxyquinoxaline dissolved in 1000 ml. of ethanol, there were added 27.6 g. (0.55 mole) of hydrazine hydrate (26.8 ml.). The resulting mixture was stirred at room temperature overnight (i.e., at *ca.* 20°C for approximately 16 hours). An additional amount of hydrazine hydrate (9.0 ml.) was then added and the final reaction mixture was allowed to stir at room temperature for a period of four hours. At this point, the precipitate was filtered and washed with ethanol to ultimately afford 43.3 g. (94%) of pure 6-fluoro-2-hydrazino-3-methoxyquinoxaline, m.p. 170—174°C. (decomp.).

c) Preparation of 7-fluoro-4-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 15 g. (0.072 mole) of 6-fluoro-2-hydrazino-3-methoxyquinoxaline and 250 ml. of triethyl orthoformate was heated with mechanical stirring in a preheated oil both at 100°C. overnight (~16 hours). The resulting mixture was then cooled to room temperature, and the precipitate which formed was subsequently recovered by means of suction filtration and washed with ethanol to ultimately afford 11.3 g (72%) of pure 7-fluoro-4-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 245—246°C. (decomp.).

d) Preparation of 7-fluoro-4-hydroxy-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 11.3 g (0.52 mole) of 7-fluoro-4-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, 115 ml. of 1*N* hydrochloric acid and 345 ml. of glacial acetic acid was refluxed for a period of three hours. Upon completion of this step, the reaction mixture was cooled to room temperature and poured over ice/water. The resulting mixture was then stirred for a period of 30 minutes and thereafter filtered to remove the precipitate, which was subsequently washed with water and air-dired to ultimately afford 8.9 g. (84%) of pure 7-fluoro-4-hydroxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >300°C. Mass spectrum: m/e, 204 (P).

e) Preparation of 4-chloro-7-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline

In a flame-dried reaction flask under a dry nitrogen atmosphere, there were placed 8.9 g (0.044 mole) of 7-fluoro-4-hydroxy-[1,2,.4]triazolo[4,3-a]quinoxaline and 160 ml. of phosphorus oxychloride together with 8.9 ml. of tri-*n*-propylamine. The reaction mixture was then refluxed overnight for approximately 16 hours and finally cooled to room temperature before being poured over ice/water with mechanical stirring. The resulting aqueous mixture was then stirred at room temperature for 30 minutes and filtered, and the solid

product so obtained was subsequently washed with cold water and triturated with ethyl acetate to ultimately afford 7.0 g. (71%) of pure 4-chloro-7-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 305—308°C. Mass Spectrum: m/e, 222 (P); m/e, 224 (P + 2).

Preparation B

4-chloro-1-ethyl-7-fluoro-(1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 1-ethyl-7-fluoro-4-methoxy-[1,2,4]triazolo-[4,3-a]quinoxaline

A mixture consisting of 15 g. (0.07 mole) of 6-fluoro-2-hydrazino-3-methoxyquinoxaline, the product of Preparation A(b), and 250 ml. of triethyl orthopropionate was heated with mechanical stirring in a preheated oil bath at 100°C. overnight (~16 hours). The resulting mixture was cooled to room temperature (~20°C.) filtered and the recovered precipitate washed with ethanol to afford 11.3 g. (64%) of pure 1-ethyl-7-fluoro-4-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 200—200°C. (decomp.).

b) Preparation of 1-ethyl-7-fluoro-4-hydroxy[1,2,4]triazolo-[4,3-a]quinoxaline

A mixture consisting of 11.3 g (0.046 mole) of 1-ethyl-7-fluoro-4-methoxy-[1,2,4]triazolo[4,3-a]-quinoxaline, 115 ml. of 1*N* hydrochloric acid and 345 ml. of glacial acetic acid was refluxed for a period of three hours. Upon completion of this step, the reaction mixture was cooled to room temperature and poured over ice/water. The resulting mixture was then stirred for a period of 30 minutes, filtered and the recovered solid product subsequently washed with water and air-dried to ultimately afford 6.6 g. (62%) of pure 1-ethyl-7-fluoro-4-hydroxy[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >300°C. Mass Spectrum: m/e 232 (P); m/e, 231 (P − 1).

c) Preparation of 4-chloro-1-ethyl-7-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline

In a frame-dried reaction flask under a dry nitrogen atmosphere, there were placed 6.6 g. (0.028 mole) of 1-ethyl-7-fluoro-4-hydroxy-[1,2,4]triazolo[4,3-a]quinoxaline and 120 ml. of phosphorus oxychloride together with 6.6 ml. of tri-n-propylamine. The reaction mixture was then refluxed overnight for approximately 16 hours and finally cooled to room temperature before being poured over ice/water with mechanical stirring. The resulting aqueous mixture was then stirred at room temperature for 30 minutes and filtered, and the solid product so obtained was subsequently washed with cold water and then dissolved in ethyl acetate. The latter organic solution was then successively washed with water, saturated aqueous sodium bicarbonate solution and saturated brine before being dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was utimately obtained a tan solid product which was subsequently triturated with diethyl ether to yield 4 g. (57%) of pure 4-chloro-1-ethyl-7-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 203—205°C. Mass Spectrum: m/e, 250 (P); m/e, 252 (P + 2); m/e, 249 (P − 1).

Preparation C

4,7-Dichloro-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 2,3-dihydroxy-6-chloroquinoxaline

A mixture consisting of 100 g. (0.07 mole) of 4-chloro-1,2-phenylenediamine and 750 ml. of diethyl oxalate was refluxed overnight and for a period of approximately 16 hours. Upon completion of this step, the reaction mixture was cooled to room temperature (~20°C.), filtered and the recovered product subsequently washed with ethanol and air-dried to constant weight to ultimately afford 140 g. of pure 2,3-dihydroxy-6-chloroquinoxaline, m.p. >260°C.

b) Preparation of 2,3,6-trichloroquinoxaline

A mixture of consisting of 140 g. (0.70 mole) of 2,3-dihydroxy-6-chloroquinoxaline and 326 ml. (3.50 mole) of phosphorus oxychloride was refluxed overnight (~16 hours) and then poured over ice. The resulting aqueous mixture was then filtered, and the recovered product subsequently washed with water and air-dried prior to being dissolved in chloroform. The latter organic solution was then washed with saturated brine and air-dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was ultimately obtained a thick slurry which was recrystallized from chloroform/ethanol to afford 120 g. (74%) of pure 2,3,6-trichloroquinoxaline, m.p. 139—142°C. Mass Spectrum: m/e, 232 (P); m/e, 234 (P + 2); m/e, 236 (P + 4).

c) Preparation of 2,6-dichloro-3-methoxyquinoxaline

A slurry consisting of 11.7 g. (0.05 mole) of 2,3,6-trichloroquinoxaline in 140 ml. of methanol was heated to 50°C., at which point there was added thereto in a dropwise manner a solution consisting of 1.4 g. (0.06 mole) of sodium dissolved in 140 ml. of methanol over a period of six hours. The resulting mixture was then heated at 50°C. overnight (~16 hours), followed by a further addition of 140 mg. of sodium in 20 ml. of methanol over a period of one hour. The final reaction mixture was then heated at 50°C. for a period of two hours and cooled to room temperature. Upon completion of this step, the spent mixture was concentrated *in vacuo* and dissolved in chloroform/water. The organic phase was separated and saved, and the aqueous phase further extracted with chloroform. The various organic (i.e., chloroform) extracts were

combined and successively washed with fresh portions of water and saturated brine, followed by drying over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, the residue was chromatographed on a column of 250 ml. of silica gel and eluted with toluene. Like fractions were combined to ultimately afford a white solid consisting of 9.8 g. (86%) of pure 2,6-dichloro-3-methoxyquinoxaline, m.p. 92—95°C.

d) Preparation of 6-chloro-2-hydrazino-3-methoxyquinoxaline

A mixture of 4.9 g. (0.02 mole) of 2,6-dichloro-3-methoxyquinoxaline and 2.7 g. (0.053 mole) of hydrazine hydrate (2.6 ml.) in 75 ml. of ethanol was stirred at room temperature overnight (i.e., at *ca.* 20°C. for approximately 16 hours). Upon completion of this step, the resulting mixture was filtered and the recovered precipitate was washed with ethanol to ultimately afford 4.4 g. (98%) of pure 6-chloro-2-hydrazino-3-methoxyquinoxaline, m.p. 175—179°C. (decomp.). Mass Spectrum: m/e, 224 (P); m/e, 226 (P + 2).

e) Preparation of 7-chloro-4-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 1.4 g. (0.0062 mole) of 6-chloro-2-hydrazino-3-methoxyquinoxaline and 20 ml. of triethyl orthoformate was heated with mechanical stirring in a preheated oil bath at 100°C. overnight (~16 hours). The resulting mixture was then cooled to room temperature, and the precipitate which formed was subsequently recovered by means of suction filtration and washed with ethanol to ultimately afford 1.0 g. (69%) of pure 7-chloro-4-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 250—252°C.

f) Preparation of 7-chloro-4-hydroxy-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 3.4 g. (0.014 mole) of 7-chloro-4-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, 35 ml. of 1*N* hydrochloric acid and 105 ml. of glacial acetic acid was refluxed for a period of 2.5 hours. Upon completion of this step, the reaction mixture was cooled to room temperature and poured over ice/water. The resulting mixture was then stirred for a period of 20 minutes, filtered and the recovered solid product washed with water and air-dried to constant weight to ultimately afford 2.6 g. (87%) of pure 7-chloro-4-hydroxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >300°C.

g) Preparation of 4,7-dichloro-[1,2,4]triazolo[4,3-a]quinoxaline

In a flame-dried reaction flask under a dry nitrogen atmosphere, there were placed 2.6 g. (0.012 mole) of 7-chloro-4-hydroxy-[1,2,4]-triazolo[4,3-a]quinoxaline and 40 ml. of phosphorus oxychloride together with 2.6 ml. of tri-n-propylamine. The reaction mixture was then refluxed overnight for approximately 16 hours and finally cooled to room temperature prior to being slowly poured over ice/water. The resulting aqueous mixture was next extracted with ethyl acetate and the latter extract was successively washed with water, saturated aqueous sodium bicarbonate solution and saturated brine before being dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was ultimately obtained a yellowish solid product as residue which was subsequently chromatographed on a 200 ml. silica gel column and then eluted with chloroform/methanol (9:1 by volume). Like fractions were then combined and concentrated *in vacuo* to finally afford an orange solid product which consisted of 1.89 g. (66%) of pure 4,7-dichloro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 253—256°C. (decomp.). Mass Spectrum: m/e, 238 (P); m/e, 240 (P + 2); m/e, 242 (P + 4).

Preparation D

4,7-Dichloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 7-chloro-1-ethyl-4-methoxy-[1,2,4]triazolo-[4,3-a]quinoxaline

A mixture consisting of 5.1 g. (0.022 mole) of 6-chloro-2-hydrazino-3-methoxyquinoxaline, the product of Preparation C(d), and 60 ml. of triethyl orthopropionate was heated with mechanical stirring in a preheated oil bath at 100°C. overnight (~16 hours). The resulting mixture was then cooled to room temperature (~20°C.), and the precipitate which formed was subsequently collected by means of suction filtration and washed with diethyl ether to ultimately afford 4.3 g. (75%) of pure 7-chloro-1-ethyl-4-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 221—223°C.

b) Preparation of 7-chloro-1-ethyl-4-hydroxy-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 4.3 g. (0.0072 mole) of 7-chloro-1-ethyl-4-hydroxy-[1,2,4]triazolo[4,3-a]quinoxaline, 40 ml. of 1*N* hydrochloric acid and 60 ml. of methanol was refluxed overnight and then cooled to room temperature. The precipitate which formed was subsequently collected by means of suction filtration and washed with methanol. In this manner, there was ultimately obtained 3.7 g. (94%) of pure 7-chloro-1-ethyl-4-hydroxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >300°C.

c) Preparation of 4,7-dichloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

In a flame-dried reaction flask under a dry nitrogen atmosphere, there were placed 5.1 g (0.02 mole) of 7-chloro-1-ethyl-4-hydroxy-[1,2,4]triazolo[4,3-a]quinoxaline and 75 ml. of phosphorus oxychloride together

with 5 ml. and tri-n-propylamine. The reaction mixture was then refluxed overnight for approximately 16 hours and finally cooled to room temperature prior to being slowly poured over ice/water. The resulting aqueous mixture was next stirred at room temperature for 15 minutes and filtered, and the solid product so obtained was subsequently washed with cold water and air-dried to constant weight to ultimately afford 4.2 g. (79%) of pure 4,7-dichloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 217—220°C. (decomp.). Mass Spectrum: m/e 266 (P); m/e, 268 (P + 2); m/e, 265 (P − 1).

Preparation E

4-Chloro-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 2,3-dihydroxy-6-methoxyquinoxaline

A mixture consisting of 20 g. (0.114 mole) of 4-methoxy-*o*-phenylenediamine and 11 g. (0.114 mole) of triethylamine dissolved in 200 ml. of diethyl oxalate was refluxed overnight for a period of approximately 16 hours. Upon completion of this step, the reaction mixture was cooled to room temperature (20°C.) and filtered to remove the desired product. After washing with ethanol, there were ultimately obtained 14.8 g. (68%) of pure 2,3-dihydroxy-6-methoxyquinoxaline, m.p. >300°C. Mass Spectrum: m/e, 192 (P).

b) Preparation of 2,3-dichloro-6-methoxyquinoxaline

In a flame-dried reaction flask under a dry nitrogen atmosphere, there were placed 14.8 g. (0.077 mole) of 2,3-dihydroxy-6-methoxyquinoxaline and 75 ml. of phosphorus oxychloride together with 15 ml. of tri-n-propylamine. The exothermic reaction mixture was then allowed to stir at room temperature (20°C.) for a period of one hour and thereafter was refluxed overnight (~16 hours). Upon completion of this step, the reaction mixture was again cooled to room temperature and finally poured slowly over ice/water. The resulting aqueous mixture was then stirred at room temperature for a period of 20 minutes, filtered and the recovered precipitate washed with water prior to being dissolved in chloroform. The latter solution was then filtered to remove insoluble material and the filtrate so obtained was successively washed with water, saturated sodium bicarbonate solution and saturated brine. Concentration of the washed solution *in vacuo*, followed by recrystallization of the residue from ethanol, then gave 14.2 g. (80%) of pure 2,3-dichloro-6-methoxyquinoxaline, m.p. 156—159°C. Mass Spectrum: m/e, 228 (P); m/e, 230 (P + 2); m/e, 232 (P + 4).

c) Preparation of 2-chloro-3,6-dimethoxyquinoxaline

In a flame-dried reaction flask under a dry nitrogen atmosphere, there was slowly added a solution consisting of 850 mg. of sodium dissolved in 80 ml. of methanol to a slurry of 7.1 g. of 2,3-dichloro-6-methoxyquinoxaline in 60 ml. of methanol at 50°C. over a period of seven hours. The resulting mixture was then heated at 50°C. overnight and finally cooled to room temperature. Upon completion of this step, the spent reaction mixture was concentrated *in vacuo* and the residue subsequently dissolved in chloroform, followed by washing with water and drying over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, the resulting residue was subsequently chromatographed on a column of 400 ml. of silica gel, followed by elution with toluene. The good fractions were combined and concentrated *in vacuo* to ultimately afford a white solid consisting of 6.1 g (88%) of pure 2-chloro-3,6-methoxyquinoxaline. m.p. 79—81°C.

Anal. Calcd. for $C_{10}H_9ClN_2O_2$: C, 53.47; H, 4.04; N, 12.47.
Found: C, 53.29; H, 4.05; N, 12.28.

d) Preparation of 3,6-dimethoxy-2-hydrazinoquinoxaline

A mixture consisting of 5 g. (0.022 mole) of 2-chloro-3,6-dimethoxyquinoxaline and 2.8 g. (0.056 mole) of hydrazine hydrate (2.7 ml.) in 75 ml. of ethanol was heated at 50°C. overnight. Upon completion of this step, a further 1.0 ml. of hydrazine hydrate was added to the mixture and the resulting mixture was heated at 50°C. for a period of six hours. At this point, another 1.0 ml. of hydrazine hydrate was added and the final reaction mixture was heated at 50°C. overnight prior to being cooled to room temperature. The spent mixture was then filtered and the recovered precipitate washed with ethanol to ultimately afford 4.1 g. (85%) of pure 3,6-dimethoxy-2-hydrazinoquinoxaline, m.p. 128—130°C. (decomp.).

e) Preparation of 4,7-dimethoxy-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 1.5 g. (0.068 mole) of 3,6-dimethoxy-2-hydroazinoquinoxaline and 20 ml. of triethylorthoformate was heated with mechanical stirring in a preheated oil bath at 100°C. overnight (16 hours). The resulting mixture was then cooled to room temperature, and the precipitate which formed was subsequently recovered by means of suction filtration and washed with ethanol to ultimately afford 1.8 g. of pure 4,7-dimethoxy[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 238—240°C. (decomp.). Mass Spectrum: m/e, 230 (P); m/e, 231 (P + 1); m/e, 232 (P + 2).

f) Preparation of 4-hydroxy-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 1.6 g. (0.0069 mole) of 4,7-dimethoxy-([1,2,4]triazolo[4,3-a]quinoxaline, 16 ml. of 1*N* hydrochloric acid and 48 ml. of glacial acetic acid was refluxed for a period of three hours. Upon completion of this step, the reaction mixture was poured over ice and filtered. The recovered product was

then collected on the filter funnel and washed with diethyl ether to ultimately afford 1.19 g. (80%) of pure 4-hydroxy-7-methoxy[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >250°C.

g) Preparation of 4-chloro-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline

In a flame-dried reaction flask under a dry nitrogen atmosphere, there were placed 1.1 g. (0.0055 mole) of 4 hydroxy-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline and 15 ml. of phosphorus oxychloride together with 1.0 ml. of tri-n-propylamine. The reaction mixture was then refluxed overnight for approximately 16 hours and finally cooled to room temperature prior to being slowly poured over ice/water. The resulting aqueous mixture was next extracted with ethyl acetate, and the latter extract was successively washed with water and saturated brine before being dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was ultimately obtained a residual product that was subsequently chromatographed on a 150 ml. silica gel column and then eluted with chloroform/methanol (95:5 by volume). Like fractions containing the product were then combined and concentrated *in vacuo* to finally afford a residual material, which was recrystallized from chloroform/diethyl ether to yield 400 mg. (31%) of pure 4-chloro-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 266—268°C. (decomp.). Mass Spectrum: m/e, 234 (P); m/e, 236 (P + 2).

Preparation F

4-Chloro-1-ethyl-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 1-ethyl-4,7-dimethoxy-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 4.0 g. (0.018 mole) of 3,6-dimethoxy-2-hydrazinoquinoxaline, the product of Preparation E(d), and 50 ml. of triethyl orthopropionate was heated with mechanical stirring in a preheated oil bath at 100°C. overnight (~16 hours). The resulting reaction mixture was then cooled to room temperature (~20°C.), and the precipitate which formed was subsequently recovered by means of suction filtration and washed with ethanol to ultimately afford 3.3 g. (72%) of pure 4,7-dimethoxy-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 184—188°C. Mass Spectrum: m/e, 258 (P); m/e, 228 (P − 30).

b) Preparation of 1-ethyl-4-hydroxy-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 3.3 g. (0.013 mole) of 4,7-dimethoxy-1-ethyl-[1,2,4]triazalol[4,3-a]quinoxaline, 33 ml. of 1*N* hydrochloric acid and 99 ml. of glacial acetic acid was refluxed for a period of two hours. Upon completion of this step, the reaction mixture was cooled to room temperature and poured over ice/water. The resulting mixture was then stirred for a period of 20 minutes and extracted with ethyl acetate. The latter extract next washed with saturated brine and dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was finally obtained a yellowish solid product which was washed with water and air-dried to constant weight to ultimately afford 1.87 g. (67%) of pure 1-ethyl-4-hydroxy-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >250°C.

c) Preparation of 4-chloro-1-ethyl-7-methoxy-[1,2,4]triazolo[4,3-a]-quinoxaline

In a flame-dried reaction flask under a dry nitrogen atmosphere, there were placed 1.87 g. (0.0076 mole) of 1-ethyl-4-hydroxy-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline and 25 ml. of phosphorus oxychloride together with 1.8 ml. of tri-n-propylamine. The reaction mixture was then refluxed overnight for approximately 16 hours and finally cooled to room temperature prior to being slowly poured over ice/water. The resulting aqueous mixture was then stirred at room temperature for 30 minutes and filtered, and the solid product so obtained was subsequently washed with cold water and then dissolved in chloroform. The latter organic solution was thereafter washed with saturated brine and dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was finally obtained a yellow solid product which was triturated with diethyl ether and filtered to ultimately afford 1.6 g. (80%) of pure 4-chloro-1-ethyl-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 173—175°C. Mass Spectrum: m/e, 262 (P); m/e, 264 (P + 2); m/e, 261 (P − 1).

Preparation G

4-Chloro-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 2,3-dihydroxy-6-fluoroquinoxaline

A mixture consisting of 26.3 g. (0.19 mole) of 4-fluoro-1,2-phenylenediamine [*Journal of the American Chemical Society*, Vol. 75, P. 1294 (1953)] and 150 ml. of diethyl oxalate was refluxed under a nitrogen atmosphere for a period of 18 hours. Upon completion of this step, the reaction mixture was cooled to room temperature (~20°C.), filtered and the recovered product subsequently washed with four-100 ml. portions of ethanol and air-dried to constant weight to ultimately afford 19.3 g. (80%) of pure 2,3-dihydroxy-6-fluoroquinoxaline, m.p. >300°C. (literature m.p. 387—390°C., according to U.S. Patent No. 3,992,378). Mass Spectrum: m/e, 180 (P+).

b) Preparation of 2,3-dichloro-6-fluoroquinoxaline

A mixture consisting of 19 g. (0.105 mole of 2,3-dihydroxy-6-fluoroquinoxaline and 50 ml. of phosphorus oxychloride was refluxed overnight (~16 hours) and then cooled to room temperature prior to being poured over 200 g. of ice with good stirring. The resulting aqueous mixture was then filtered, and the recovered product subsequently washed several times with water to utimately afford 28.2 g. of 2,3-dichloro-6-fluoroquinoxaline, m.p. 148—152°C.

c) Preparation of 2-chloro-6-fluoro-3-hydrazinoquinoxaline

To a suspension of 28.2 g. (0.105 mole) of 2,3-dichloro-6-fluoroquinoxaline in 500 ml. of ethanol, there were added 15 ml. (0.31 mole) of hydrazine hydrate over a period of two minutes to give a dark red suspension. The resulting mixture was then stirred under a nitrogen atmosphere at room temeprature for a period of 20 hours. At this point, the precipitate was filtered and washed several times with ethanol, followed by air-drying to constant weight to ultimately afford 20.7 g. (93%) of pure 2-chloro-6-fluoro-3-hydrazinoquinoxaline, m.p. 190—192°C. (decomp.).

d) Preparation of 4-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 10 g. (0.047 mole) of 2-chloro-6-fluoro-3-hydrazinoquinoxaline and 80 ml., (0.47 mole) of triethyl orthoformate was heated under a nitrogen atmosphere with mechanical stirring in a preheated oil bath at 100°C. overnight (~16 hours). The resulting mixture was cooled to room temperature, and the precipitate which formed was subsequently recovered by means of suction filtration, washed with three-50 ml. portions of ethanol and air-dried to constant weight to ultimately afford 9.42 g. (91%) of pure 4-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 310—312°C. (decomp.). Mass Spectrum: m/e, 224, 223, 222 (P+).

Preparation H

4-Chloro-1-ethyl-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 10.0 g. (0.047 mole) of 2-chloro-6-fluoro-3-hydrazinoquinoxaline, the product of Preparation G(c), and 95 ml. (0.47 mole) of triethyl orthpropionate was heated under a nitrogen atmosphere with mechanical stirring in a preheated oil bath at 100°C. overnight (~16 hours). The resulting mixture was cooled to room temperature (~20°C.), and the precipitate which formed was subsequently recovered by means of suction filtration, washed with three 50 ml. portions of ethanol and air-dried to constant weight to ultimately afford 7.5 g. (65%) of pure 4-chloro-1-ethyl-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 160—163°C. (decomp.). Mass Spectrum: m/e, 249, 250, 251, 252 (P+).

Preparation I

4-Chloro-8-fluoro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 8-fluoro-4-hydroxy-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 12.8 g. (0.06 mole) of 2-chloro-6-fluoro-3-hydrazinoquinoxaline in 50 ml. (0.65 mole) of trifluoroacetic acid was heated under a dry nitrogen atmosphere at 120°C. for a period of 24 hours with the aid of mechanical stirring to give a homogeneous solution. The resulting reaction mixture was then poured with stirring over ice/water, stirred for an additional 30 minutes and filtered. The product so obtained was thereafter washed with three-separate portions of water and dried *in vacuo* at 80°C. to ultimately afford 12.58 g. (77%) of pure 8-fluoro-4-hydroxy-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]-quinoxaline, m.p. 298—302°C. Mass Spectrum: m/e, 272 (P+).

b) Preparation of 4-chloro-8-fluoro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline

In a flame-dried 250 ml. three-necked reaction flask under a dry nitrogen atmosphere, there were placed 12.5 g. (0.046 mole) of 8-fluoro-4-hydroxy-1-trifluoromethyl-[1,2,4]-triazolo(4,3-a]quinoxaline and 85 ml. of phosphorus oxychloride together with 17.5 ml. of tri-n-propylamine. The reaction mixture was then refluxed overnight for approximately 16 hours and finally cooled to room temperature (~ 20°C.) prior to being slowly poured over 1000 ml. of ice/water with the aid of mechanical stirring. The resulting aqueous mixture was next stirred for an additional period of 30 minutes at room temperature, followed by extraction with three-300 ml. portions of chloroform. The combined chloroform layers were then successively washed with saturated aqueous sodium bicarbonate solution, water and saturated brine and finally dried over anhydrous magnesium sulfate.

After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was finally obtained a yellow solid product which consisted of 10.47 g. (79%) of pure 4-chloro-8-fluoro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 135—138°C. Mass Spectrum: m/e, 292/290 (P+).

Preparation J

4-Chloro-7,8-difluoro-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 2,3-dihydroxy-6,7-difluoroquinoxaline

A mixture consisting of 11.3 g. (0.0784 mole) of 4,5-difluoro-*o*-phenylenediamine (U.S. Patent No. 4,284,600) and 80 ml. (0.589 mole) of diethyl oxalate was refluxed for a period of four hours to give a thick

precipitate of product. The spent reaction mixture was then cooled to room temperature (20°C.) overnight, filtered and the solid product so obtained was thereafter washed several times with diethyl ether and air-dried to constant weight to ultimately afford 15.5 g of pure 1,3-dihydroxy-6,7-difluoroquinoxaline, m.p. >310°C. Mass Spectrum: m/e, 198 (P+).

b) Preparation of 2,3-dichloro-6,7-difluoroquinoxaline

A mixture consisting of 15.4 g. (0.078 mole) of 2,3-dihydoxy-6,7-difluoroquinoxaline, 39 g. (0.187 mole) of phosphorus pentachloride and 20 ml. (0.22 mole) of phosphorus oxychloride was refluxed with stirring for a period of four hours, during which time an additional amount of 20 ml. of phosphorus oxychloride was added to facilitate the stirring (the reaction mixture become homogeneous within 30 minutes). Upon completion of this step, the reaction mixture was stirred overnight (16 hours) at room temperature to give a light yellow precipitate. The spent mixture was then poured over 200 g. of ice/water and further stirred with additional cooling to give a tan solid which consisted of 20.9 g of 2,3-dichloro-6,7-difluororquinoxaline, m.p. 162—164°C. (decomp.). Mass Spectrum: m/e, 238/236/234 (P+).

c) Preparation of 2-chloro-6,7-difluoro-3-hydrazinoquinoxaline

A mixture consisting of 10 g. (0.0426 mole) of 2,3-dichloro-6,7-difluoroquinoxaline and 5 ml. (0.03 mole) of hydrazine hydrate in 200 ml. of ethanol was stirred at room temperature for a period of 24 hours to give a rust-red precipitate. The thick slurry was filtered and the recovered product washed with two-20 ml. portions of ethanol, followed by air-drying to constant weight to ultimately afford 5.99 g. (67%) of pure 2-chloro-6,7-difluoro-3-hydrazinoquinoxaline, m.p. 212—215°C. (decomp.). Mass Spectrum: m/e, 230 (P); m/e, 232 (P+).

d) Preparation of 4-chloro-7,8-difluoro-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 5.99 g. (0.026 mole) of 2-chloro-6,7-difluoro-3-hydrazinoquinoxaline and 30 ml. (0.18 mole) of triethyl orthoformate was heated at 100°C. for a period of 24 hours to give a red-brown solid. The resulting slurry was then cooled to room temperature and filtered, and the recovered product subsequently washed with diethyl ether to ultimately afford 5.15 g. (82%) of pure 4-chloro-7,8-difluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >210°C. (decomp.). Mass Spectrum: m/e, 242/240 (P+).

Preparation K

4-Chloro-6,7-difluoro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 7.0 g. (0.03 mole) of 2-chloro-6,7-difluoro-3-hydrazinoquinoxaline, the product of Preparation J(c), and 60 ml. (0.30 mole) of triethyl orthopropionate was heated under a nitrogen atmosphere with mechanical stirring in a preheated oil bath at 100°C. for a period of 24 hours. The resulting mixture was cooled to room temperature (~20°C.), and the red precipitate which formed was subsequently recovered by means of suction filtration, washed with two separate portions of diethyl ether and air-dried to constant weight to ultimately afford 4.15 g (52%) of pure 4-chloro-6,7-difluoro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 185—186°C. (decomp.).

Preparation L

4,8-Dichloro-1-methyl-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 2,6-dichloro-6-hydrazinoquinoxaline

A mixture consisting of 23 g. (0.10 mole) of 2,3,6-trichloroquinoxaline and 11 g. (0.22 mole) of hydrazine hydrate in 500 ml. of ethanol was stirred at room temperature (~ 20°C.) overnight (~ 16 hours). The precipitate which formed was separated by filtration and washed with ethanol to ultimately afford 22.2 g. (97%) of pure 2,6-dichloro-3-hydrazinoquinoxaline, m.p. >250°C. Mass Spectrum: m/e, 228 (P).

b) Preparation of 4,8-dichloro-1-methyl-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 20 g. (0.087 mole) of 2,6-dichloro-3-hydrazinoquinoxaline and 160 ml. (0.87 mole) of triethyl orthoacetate was heated with mechanical stirring under a dry nitrogen atmosphere in a preheated oil bath at 100°C. for a period of 20 hours to give a yellow suspension. The resulting mixture was cooled to room temperature and filtered, and the recovered solid product was subsequently washed with ethanol and air-dried to constant weight to ultimately afford 10.2 g. (46%) of pure 4,8-dichloro-1-methyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >280°C. Mass Spectrum: m/e, 254/252 (P+).

Preparation M

4,8-Dichloro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 8-chloro-4-hydroxy-1-trifluoromethyl[1,2,4]triazolo[4,3-a]quinoxaline

In a flame-dried 500 ml. three-necked reaction flask equipped with mechanical stirrer, nitrogen-inlet tube and reflux condenser, there were placed 67 ml. (0.87 mole) of trifluoroacetic acid. Stirring was commenced and 20 g. (0.087 mole) of 2,6-dichloro-3-hydrazinoquinoxaline, the product of Preparation L(a) were added thereto. The resulting reaction mixture was then heated on a steam bath for a period of 24 hours, cooled to room temperature (~20°C.) and poured over 200 g. of ice/water. The aqueous mixture so

obtained was then stirred for 30 minutes, filtered and the recovered product subsequently washed several times with water and air-dried to constant weight (required approximately 18 hours). In this way, there were ultimately obtained 14.3 g. (57%) of pure 8-chloro-4-hydroxy-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]-quinoxaline, m.p. 253—255°C. (decomp.) Mass Spectrum: m/e, 290/288 (P+).

b) Preparation of 4,8-dichloro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline

In a flame-dried 250 ml. three-necked reaction flask equipped with mechanical stirrer, dropping funnel and reflux condenser, under a nitrogen sweep, there were placed 14.3 g. (0.05 mole) of 8-chloro-4-hydroxy-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline in 100 ml. of phosphorus oxychloride. To the resulting suspension, there were then added in a dropwise manner 19 ml. (0.10 mole) of tri-n-propylamine over a period of five minutes. The resulting reaction mixture was then refluxed for a period of 20 hours to give a clear dark wine-red solution. Upon completion of this step, the clear solution so obtained was cooled to room temperature and poured over 1000 ml. of ice/water with the aid of strong mechanical stirring. The resulting aqueous mixture was then stirred at room temperature for a period of 30 minutes and next extracted with three-500 ml. portion of chloroform. The latter organic extracts were subsequently combined and then successively washed with water, saturated aqueous sodium bicarbonate solution, water and saturated brine, followed by drying over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was finally obtained a yellow solid which consisted of 11.4 g. (75%) of pure 4,8-dichloro-1-trifluoro-methyl[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 133—135°C. Mass Spectrum: m/e, 308 (P + 2); m/e, 310 (P + 4).

Preparation N

4,8-Dichloro-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline

In a 250 ml. three-necked reaction flask equipped with mechanical stirrer and reflux condenser, there were placed 50.0 g. (0.274 mole) of trimethyl orthobenzoate that had been preheated at *ca.* 70°C. Stirring was commenced and 10.0 g (0.0437 mole) of 2,6-dichloro-3-hydrazinoquinoxaline, the product of Preparation L(a), were added thereto. The resulting reaction mixture was then heated at *ca.* 120°C., with continued stirring, for a period of 24 hours, followed by cooling to room temperature (20°C.) and stirring overnight for approximately 16 hours to give a yellow slurry. The latter slurry was then filtered, and the recovered solid product was subsequently washed with two-50 ml. portions of ethanol and air-dried to constant weight to ultimately afford 9.8 g. (72%) of crude 4,8-dichloro-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 305—307°C. Mass Spectrum: m/e, 316/314 (P+).

Example 1

2-Chloro-3-hydrazinoquinoxaline

2,3-Dichloroquinoxaline (33.5 g., 0.168 mole) was stirred with hydrazine hydrate (18.5 g., 0.369 mole) in 500 ml. of ethanol at room temperature overnight (i.e., at *ca.* 20°C. for approximately 16 hours). The thick, yellow slurry was filtered and the precipitate was washed with ethanol. The precipitated material was recrystallized from hot methanol to give 13.5 g. (41% yield) of 2-chloro-3-hydrazinoquinoxaline, m.p. 181°C. (decomp.). Mass spectrum: m/e, 194 (P).

Example 2

4-Chloro-[1,2,4]triazolo[4,3-a]quinoxaline

2-Chloro-3-hydrazinoquinoxaline (9.0 g., 0.046 mole), the product of Example 1, was stirred with triethyl orthoformate (90 ml.) at 100°C. for one hour. The mixture was cooled to room temperature and the solid precipitate was collected by filtration and washed with cyclohexane and dried to afford 8.8 g. (94% yield) of 4-chloro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 287—290°C. (decomp.). Mass spectrum: m/e, 204 (P).

Example 3

4-Chloro-1-methyl-[1,2,4]triazolo[4,3-a]quinoxaline

2-Chloro-3-hydrazinoquinoxaline (15.5 g., 0.080 mole), the product of Example 1, was stirred with triethyl orthoacetate for 3 hours at 100°C. The mixture was cooled to room temperature and the solid precipitate was collected by filtration, washed with ethanol and air dried to afford 11.4 g. (65% yield) of 4-chloro-1-methyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 215—222°C. Mass spectrum: m/e, 218 (P).

Example 4

4-Chloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

2-Chloro-3-hydrazinoquinoxaline (4.5 g., 0.023 mole), the product of Example 1, was stirred with triethyl orthopropionate (50 ml.) at 100°C. for one hour. The mixture was cooled to room temperature and the white precipitate was collected by filtration and washed with cyclohexane to give 4.5 g. (85% yield) of 4-chloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 158—160°C. Mass spectrum: m/e, 232 (P).

Example 5

4-Chloro-1-n-propyl-[1,2,4]triazolo[4,3-a]quinoxaline

2-Chloro-3-hydrazinoquinoxaline (3.0 g., 0.015 mole), the product of Example 1, was stirred with triethyl orthobutyrate (27 ml.) at 100°C. for 2 hours. The mixture was cooled to room temperature, and the precipitate was collected by filtration and washed with cyclohexane. The crude solid was taken up in chloroform and filtered to remove insoluble material. The chloroform solution was concentrated *in vacuo* to give a solid which was recrystallized from chloroform to give 1.96 g. (53% yield) of 4-chloro-1-n-propyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 173—175°C. Mass spectrum: m/e, 246 (P).

Example 6

4-Chloro-1-isopropyl-[1,2,4]triazolo[4,3-a]quinoxaline

2-Chloro-3-hydrazinoquinoxaline (4.0 g., 0.02 mole), the product of Example 1, was stirred with triethyl orthoisobutyrate (15 ml.) at 100°C. for three hours. The solution was cooled to room temperature and the precipitate was collected by filtration and washed with ethanol. The crude solid was recrystallized from 300 ml. of hot ethanol to afford 2.06 g. (40% yield) of 4-chloro-1-isopropyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 208—210°C. Mas spectrum: m/e 246 (P).

Example 7

4-Methylamino-[1,2,4]triazolo[4,3-a]quinoxaline

4-Chloro-[1,2,4]triazolo-[4,3-a]quinoxaline (2.0 g., 0.01 mole), the product of Example 2, in N,N-dimethylformamide (30 ml.) was saturated with monomethylamine gas and stirred at room temperature for 3 hours. Monomethylamine gas was again bubbled into the solution and the solution was stirred at room temperature for an additional 2 hours. The precipitate was separated by filtration and washed with N,N-dimethylformamide. Recrystallization from N,N-dimethylformamide gave 1.37 g. (69% yield) of 4-methylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >300°C. Mass spectrum: m/e, 199 (P).

Anal. Calcd. for $C_{10}H_9N_5$: C, 60.29; H, 4.55; N, 35.15.
Found: C, 59.99; H, 4.47; N, 35.11.

Example 8

4-Dimethylamino-[1,2,4]triazolo[4,3-a]quinoxaline

A slurry of 2.0 g (0.01 mole) of 4-chloro-[1,2,4]triazolo[4,3-a]quinoxaline (the product of Example 2) in N,N-dimethylformamide (30 ml.) was saturated with dimethylamine gas and stirred at room temperature overnight. The mixture was poured over ice and the precipitate was removed by filtration. Recrystallization from ethanol gave 640 mg. (44% yield) of 4-dimethylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 184—186°C. Mass spectrum: m/e, 213 (P).

Anal. Calcd. for $C_{11}H_{11}N_5$: C, 61.96; H, 5.20; N, 32.84.
Found: C, 62.26; H, 5.43; N, 32.92.

Example 9

4-Ethylamino-[1,2,4]triazolo[4,3-a]quinoxaline

A slurry of 2.0 g. (0.01 mole) of 4-chloro-[1,2,4]triazolo[4,3-a]quinoxaline (the product of Example 2) in N,N-dimethlformamide (30 ml.) was saturated with monoethylamine gas and stirred at room temperature for 2 hours. Monoethylamine gas was again bubbled through the mixture and stirring was continued for 2 hours. The precipitate was removed by filtration and washed wtih N,N-dimethylformamide. Recrystallization from methanol afforded 680 mg. (32% yield) 4-ethylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 254—6°C. Mass spectrum: m/e, 213 (P).

Anal. Calcd. for $C_{11}H_{11}N_5$: C, 61.96; H, 5.20; N, 32.84.
Found: C, 61.93; H, 5.09; N, 32.72.

Example 10

4-Diethylamino-[1,2,4]triazolo[4,3-a]quinoxaline

4-Chloro-[1,2,4]triazolo[4,3-a]-quinoxaline (4.4 g., 0.021 mole), the product of Example 2, was stirred with diethylamine (6.5 ml., 0.063 mole) in N,N-dimethylformamide (100 ml.) at room temperature for 2 hours. The reaction mixture was poured over an ice-water mixture to form a crude precipitate as product, which was subsequently filtered and washed with water. Recystallization from isopropanol gave 3.36 g. (66% yield) of 4-diethylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 117—119°C. Mass spectrum: m/e, 241 (P).

Example 11

4-Di-n-propylamino-[1,2,4]triazolo[4,3-a]quinoxaline

4-Chloro-[1,2,4]triazolo[4,3-a]-quinoxaline (2.0 g., 0.01 mole), the product of Example 2, and 3.0 g. (0.03 mole) of di-n-propylamine in N,N-dimethylformamide (50 ml.) were stirred for 3 hours at room

temperature. The solution was poured over ice to form a precipitate which was separated by filtration and air dried. Recrystallization from cyclohexane (250 ml.) afforded 1.1 g (41% yield) of 4-di-n-propylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 240—242°C. Mass spectrum: m/e, 269 (P).

Anal. Calcd. for $C_{15}H_{19}N_5$: C, 66.89; H, 7.11; N, 26.00.
Found: C, 66,68; H, 6.97; N, 26.12.

Example 12

4-Isopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline

4-Chloro-[1,2,4]triazolo[4,3-a]-quinoxaline (2.0 g., 0.01 mole), the product of Example 2, and 1.77 g. (0.03 mole) of isopropylamine in N,N-dimethylformamide (30 ml.) were stirred at room temperature overnight. The dark solution was poured over ice and the precipitate which was produced was separated by filtration and washed with water. The crude product was recrystallized from ethanol and then twice from isopropyl ether to afford 1.2 g. (53% yield) of 4-isopropylamino-[1,2,4]-triazolo[4,3-a]quinoxaline, m.p. 133—5°C. Mass spectrum: m/e 222 (P).

Anal. Calcd. for $C_{12}H_{13}N_5 \cdot \frac{1}{3}H_2O$: C, 61.79; H, 5.90; N, 30.02.
Found: C, 61.51; H, 5.89; N, 29.90

Example 13

4-Diethylamino-1-methyl-[1,2,4]triazolo[4,3-a]quinoxaline

This compound was prepared by the method of Example 11, utilizing 4-chloro-1-methyl-[1,2,4]triazolo-[4,3-a]quinoxaline (the product of Example 3) as starting material in place of 4-chloro-[1,2,4]triazolo[4,3-a]-quinoxaline (the product of Example 2) and diethylamine as reagent in place of di-n-propylamine. The crude product obtained was recrystallized from chloroform and then from cyclohexane to afford 7.2 g. (54% yield) of pure 4-diethylamino-1-methyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 123—5°C.

Example 14

4-Amino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

Ammonia gas was bubbled through a solution of 1.2 g. (0.005 mole) of 4-chloro-1-ethyl-[1,2,4]triazolo-[4,3-a]quinoxaline (the product of Example 4) in N,N-dimethylformamide (20 ml.) at 0°C. for about 2 minutes. The solution was stirred at 0°C. for 30 minutes and at room temperature for one hour. The reaction mixture was then poured over ice and stirred for 20 minutes. The precipitate which formed was removed by filtration, washed with water and air dried. Recrystallization from ethanol afforded 220 mg. (22% yield) of pure 4-amino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 284—8°C. Mass spectrum: m/e, 213 (P).

Anal. Calcd. for $C_{11}H_{11}N_5 \cdot \frac{1}{6}H_2O$: C, 61.10; H, 5.28; N, 32.39.
Found: C, 61.36; H, 5.14; N, 31.96.

Example 15

4-Methylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

Monomethylamine gas was bubbled through a solution of 4-chloro-1-ethyl-[1,2,4]triazolo[4,3-a]-quinoxaline [1.2 g., 0.005 mole), the product of Example 4, in N,N-dimethylformamide (50 ml.) at 0°C. for 2 minutes. The reaction mixture was stirred at 0°C. for 30 minutes, at room temperature for 2 hours, and then poured over ice and stirred another 20 minutes. The precipitate which formed was separated by filtration, washed with water and air dried. Recrystallization from ethanol then afforded 1.0 g. (88% yield) of 4-methylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 271—3°C. Mass spectrum: m/e, 227 (P).

Anal. Calcd. for $C_{12}H_{13}N_5 \cdot \frac{1}{3}H_2O$: C, 62.80; H, 5.82; N, 30.51.
Found: C, 62.72; H, 5.86; N, 30.62.

Example 16

4-Dimethylamino-1-ethyl[1,2,4]triazolo[4,3-a]quinoxaline

4-Chloro-1-ethyl-[1,2,4]triazolo-[4,3-a]quinoxaline (1.2 g., 0.005 mole), the product of Example 4, and 676 mg. (0.015 mole) of anhydrous dimethylamine in N,N-dimethylformamide (50 ml.) were stirred at 0°C. for 30 minutes and at room temperature for 2 hours. The reaction mixture was poured over ice and stirred for 20 minutes. The precipitate which formed was separated by filtration, washed wiht water and air dried. Recrystallization from chloroform and then from chloroform/cyclohexane afforded 510 mg. (42% yield) of 4-dimethylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 155—8°C. Mass spectrum: m/e, 241 (P).

Anal. Calcd. for $C_{13}H_{15}N_5$: C, 64.71; H, 6.27; N, 29.02.
Found: C, 64.69; H, 6.27; N, 29.32.

Example 17

1-Ethyl-4-ethylamino-[1,2,4]triazolo[4,3-a]quinoxaline

Monoethylamine was bubbled through a solution of 4-chloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline (1.2 g., 0.005 mole), the product of Example 4, in N,N-dimethylformamide (50 ml.) at 0°C. for about 2 minutes. The clear solution was stirred at 0°C. for 30 minutes and at room temperature for 2 hours. The reaction mixture was next poured over ice and the precipitate was separated by filtration, washed with water and air dried. Recrystallization from ethanol then afforded 1.0 g. (83% yield) of pure 1-ethyl-4-ethylamino-[1,2,4]triazolo[4,3-a]quinoxaline as a white solid (m.p. 235—238°C.). Mass spectrum: m/e, 241 (P).

Anal. Calcd. for $C_{13}H_{15}N_5$: C, 64.71; H, 6.27; N, 29.02.
Found: C, 64.57; H, 6.20; N, 29.15.

Example 18

4-Diethylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

This compound was prepared by the method of Example 11, utilizing 4-chloro-1-ethyl-[1,2,4]triazolo-[4,3-a]quinoxaline (the product of Example 4) as starting material in place of 4-chloro-[1,2,4]triazolo[4,3-a]-quinoxaline (the product of Example 2) and diethylamine as reagent in place of di-n-propylamine. The crude product was recrystallized from cyclohexane to afford 3.54 g. (69% yield) of pure 4-diethylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline as a white solid (m.p. 98—100°C.). Mass spectrum: m/e, 269 (P).

Example 19

4-Isopropylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

Isopropylamine (1.77 g., 0.03 mole) was added to a solution of 4-chloro-1-ethyl-[1,2,4]triazolo-[4,3-a]-quinoxaline (2.3 g., 0.01 mole), the product of Example 4, in N,N-dimethylformamide (30 ml.). Within 30 minutes, a precipitate formed. The reaction mixture was then stirred overnight at room temperature. The precipitate was separated by filtration and washed with N,N-dimethylformamide. Recrystallization from ethanol then gave 1.6 g. (63% yield) of 4-isopropoylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 222—4°C. Mass spectrum: m/e, 255 (P).

Anal. Calcd. for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43.
Found: C, 65,32; H, 6.76; N, 27.25.

Example 20

4-Ethylamino-1-isopropyl-[1,2,4]triazolo[4,3-a]quinoxaline

A slurry of 1.0 g. (0.004 mole) of 4-chloro-1-isopropyl-[1,2,4]triazolo[4,3-a]quinoxaline (the product of Example 6) in N,N-dimethylformamide (15 ml.) was saturated with monoethylamine gas and stirred at room temperature for 4 hours. The precipitate was separated by filtration and washed with N,N-dimethylformamide to afford 220 mg. (22% yield) of 4-ethylamino-1-isopropyl[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 209—211°C. Mass spectrum: m/e, 255 (P).

The filtrate was next poured over ice and the precipitate was separated by means of filtration, washed with water and recrystallized from methanol and then from isopropanol to afford another 200 mg. (20% yield) of pure 4-ethylamino-1-isopropyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 210—211°C.

Anal. Calcd. for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43.
Found: C, 65.53; H, 6.58; N, 27.29.

Example 21

4-Diethylamino-1-isopropyl-[1,2,4]triazolo[4,3-a]quinoxaline

4-Chloro-1-isopropyl-[1,2,4]-triazolo[4,3-a]quinoxaline (1.0 g., 0.004 mole), the product of Example 6, and 900 mg. (0.012 mole) of diethylamine in N,N-dimethylformamide (15 ml.) were stirred at room temperature for 4 hours. The reaction mixture was poured over ice and the precipitate was separated by means of filtration, washed with water and placed on a column of silica gel (175 ml.) and finally eluted with chloroform. The eluant was evaporated *in vacuo* to afford 850 mg. (75% yield) of pure 4-diethylamino-1-isopropyl-[1,2,4]triazolo[4,3-a]quinoxaline as a white solid (m.p. 93—95°C.). Mass spectrum: m/e, 283 (P). The pure product (100 mg.) was then distilled *in vacuo* (0.1 mm.) (13.3322 Pa.) at 140° to 150°C. to afford the analytical sample (80 mg.), m.p. 94—96°C.

Anal. Calcd. for $C_{16}H_{21}N_5$: C, 67.82; H, 7.47; N, 24.71.
Found: C, 67.56; H, 7.20; N, 24.50.

Example 22

4-Diethylamino-1-n-propyl-[1,2,4]triazolo[4,3-a]quinoxaline

4-Chloro-1-n-propyl-[1,2,4]-triazolo[4,3-a]quinoxaline (1.23 g., 0.005 mole), the product of Example 5, and 1.1 g. (0.015 mole) of diethylamine in N,N-dimethylformamide (15 ml.) were stirred at room

temperature for 2 hours. The reaction mixture was then poured over ice. The precipitate was removed by filtration, washed with water and air dried. Recrystallization (twice) from ethanol/water afforded 1.1 g. (78% yield) of pure 4-diethylamino-1-n-propyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 92—94°C.

Mass spectrum: m/e, 283 (P).

Anal. Calcd. for $C_{16}H_{21}N_5 \cdot 1/8H_2O$: C, 67.28; H, 7.50; N, 24.52.
Found: C, 67.38; H, 7.45; N, 24.73.

Example 23

8-Chloro-4-diethylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 4,8-dichloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

2,6-Dichloro-3-hydrazinoquinoxaline (1.0 g., 0.0044 mole), the product of Preparation L(a), was refluxed with 15 ml. of triethyl orthopropionate for 4 hours and cooled to room temperature. The precipitate was recovered by filtration, washed with cyclohexane and air dried to afford 730 mg. (62% yield) of 4,8-dichloro-1-ethyl[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >250°C.

Mass spectrum: m/e, 266 (P); m/e, 268 (P + 2).

b) Preparation of 8-chloro-4-diethylamino-1-ethyl-[1,2,4]triazolo-[4,3-a]quinoxaline

4,8-Dichloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline (7.4 g., 0.028 mole) and 6 g. (0.082 mole) of diethylamine in N,N-dimethylformamide (150 ml.) were stirred at room temperature for 4 hours. The reaction mixture was filtered and the filtrate was poured over ice. The precipitate which formed was then collected by means of filtration and taken up in chloroform. The chloroform layer was subsequently dried over anhydrous magnesium sulfate, filtered and then evacuated *in vacuo* to yield an off-white solid which was later recrystallized from diethyl ether/petroleum ether to afford 1.6 g. of pure 8-chloro-4-diethylamino-1-ethyl[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 105—108°C. (decomp.).

Mass Spectrum: m/e, 303 (P); m/e, 305 (P + 2).

Anal. Calcd. for $C_{15}H_{18}ClN_5$: C, 59.30; H, 5.97; N, 23.05.
Found: C, 58.92; H, 5.85; N, 22.81.

Example 24

7,8-Dichloro-4-diethylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 2,6,7-Trichloro-3-hydrazinoquinoxaline

2,3,6,7-Tetrachloroquinoxaline (4.4 g., 0.016 mole) and 1.76 g. (0.035 mole) of hydrazine hydrate in ethanol (60 ml.) were stirred overnight at room temperature. The thick slurry was filtered and washed with ethanol to afford 4.9 g. of crude 2,6,7-trichloro-3-hydrazinoquinoxaline, m.p. <260°C.

Mass spectrum: m/e, 262 (P); m/e, 264 (P + 2).

b) Preparation of 4,7,8-Trichloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

2,6,7-Trichloro-3-hydrazinoquinoxaline (4.9 g., 0.018 mole) in triethyl orthopropionate (50 ml.) was heated at 100°C. for 2 hours. The precipitate which formed was collected by means of filtration at room temperature and washed with cyclohexane. Recrystallization from chloroform/cyclohexane two times then afforded 2.9 g. (54% yield) of pure 1,7,8-trichloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline as a pink solid (m.p. 198—201°C.).

Mass spectrum: m/e, 300 (P); m/e, 302 (P + 2); m/e, 304 (P + 4); m/e, 306 (P + 6).

c) Preparation of 7,8-dichloro-4-diethylamino-1-ethyl-[1,2,4]triazolo[4,3a]quinoxaline

4,7,8-Trichloro-1-ethyl-[1,2,4]-triazolo[4,3-a]quinoxaline (2.9 g., 0.0096 mole) and 2.1 g. (0.0388 mole) of diethylamine in N,N-dimethylformamide (50 ml.) were stirred at room temperature for 2 hours. The reaction mixture was poured over ice and stirred for 15 minutes. The precipitate was separated by filtration, washed with water and air dried. Recrystallization (three times) from isopropanol then afforded 500 mg. (16% yield) of pure 7,8-dichloro-4-diethylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 147—149°C.

Mass spectrum: m/e, 337 (P); m/e, 339 (P + 2).

Anal. Calcd. for $C_{15}H_{17}Cl_2N_5$: C, 53.26; H, 5.07; N, 20.70.
Found: C, 53.05; H, 5.13; N, 20.75.

Example 25

4-Diethylamino-1-ethyl-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 2-chloro-3-hydrazino-6-methoxyquinoxaline

2,3-Dichloro-6-methoxyquinoxaline (4.2 g., 0.018 mole), the product of Preparation E(b), and 2.7 ml. of hydrazine hydrate in 100 ml. of ethanol were heated under reflux for 4 hours and stirred at room temperature overnight. The precipitate was removed by filtration and washed with ethanol to afford 3.9 g. (97% yield) of 2-chloro-3-hydrazino-6-methoxyquinoxaline, m.p. <250°C.

Mass spectrum: m/e, 224 (P); m/e 226 (P + 2).

b) Preparation of 4-chloro-1-ethyl-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline

2-Chloro-3-hydrazino-6-methoxyquinoxaline (1.3 g., 0.0058 mole) and 25 ml. of triethyl orthopropionate were heated at 100°C. for 4 hours and stirred at room temperature for 60 hours. The precipitate was removed by filtration and washed with ethanol. Recrystallization from ethanol then afforded 530 mg. (35% yield) of pure 4-chloro-1-ethyl-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 196—198°C. (decomp.).

Mass spectrum: m/e, 262 (P); m/e 264 (P + 2).

c) Preparation of 4-diethylamino-1-ethyl-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline

4-Chloro-1-ethyl-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline (520 mg., 0.002 mole) and 673 mg. (0.008 mole) of diethylamine in 10 ml. of N,N-dimethylformamide were stirred at room temperature overnight. The reaction mixture was poured over ice and the precipitate was separated by filtration, washed with water and air dried. Recrystallization from diethyl ether and petroleum ether then afforded 140 mg. (23% yield) of pure 4-diethylamino-1-ethyl-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 135—138°C.

Mass spectrum: m/e, 299 (P).

Anal. Calcd. for $C_{16}H_{21}N_5O \cdot 1/8H_2O$: C, 63.71; H, 7.10; N, 23.22.
Found: C, 63.63; H, 6.88; N, 23.37.

Example 26

4-Diethylamino-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline

a) Preparation of 4-chloro-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline

2-Chloro-3-hydrazinoquinoxaline (2.2 g., 0.011 mole) was mixed with 6 ml. of triethyl orthobenzoate and heated at 100°C. for 30 minutes. After cooling the orange mixture to room temperature, ethanol was added. Filtration of the resultant precipitate afforded 2.1 g. of crude product which was further purified by means of trituration with warm methanol, followed by filtration and air drying to ultimately yield 1.58 g. (51%) of pure 4-chloro-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline as an orange solid.

b) Preparation of 4-diethylamino-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline

To 1.58 g. (0.00563 mole) of 4-chloro-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline dissolved in 15 ml. of N,N-dimethylformamide, there was added 1.738 ml. of diethylamine. The mixture was stirred overnight at room temperature. The precipitate which formed was collected by filtration, washed with N,N-dimethylformamide and recrystallized two times from hexane/ethyl acetate (3:1 by volume) to afford 555 mg. of pure 4-diethylamino-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline in the form of white needles (m.p. 166—168°C.)

Anal. Calcd. for $C_{19}H_{19}N_5$: C, 71.60; H, 5.99; N, 22.06.
Found: C, 71.86; H, 5.86; N, 22.09.

Example 27

4-Diethylamino-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline

A) Preparation of 4-hydroxy-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline

2-Chloro-3-hydrazinoquinoxaline (3.89 g., 0.02 mole), the product of Example 1, is added to 22.8 g. (0.20 mole) of cold trifluoroacetic acid (15.4 ml.) contained in a flame-dried reaction flask surrounded by an ice bath, while under a dry nitrogen atmosphere with the aid of mechanical stirring. The reaction mixture was then heated to 100°C. for a period of 3 hours and poured over ice. The resulting product was then collected by means of suction filtration, washed with water and air dried to constant weight. In this manner, there were ultimately obtained 3.0 g. (60%) of pure 4-hydroxy-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >300°C.

Mass spectrum: m/e, 254(P).

b) Preparation of 4-chloro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline

In a flame-dried reaction flask under a dry nitrogen atmosphere, there were placed 3.0 g. (0.0118 mole) of 4-hydroxy-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline and 30 ml. of phosphorus oxychloride in 2.38 g. (0.0236 mole) of triethylamine (3.3 ml.). The reaction mixture was then heated at 100°C. for a period of approximately 16 hours (i.e., overnight). Upon completion of this step, the spent mixture was cooled to room temperature, concentrated *in vacuo* and then partitioned between ice, water and ethanol, followed by extraction with ethyl acetate. The latter extract was next washed with saturated brine and dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was obtained a residue which was subsequently dissolved in hot chloroform and filtered. The latter filtrate was then allowed to stand overnight at room temperature and filtered again. The final filtrate was then concentrated *in vacuo* to ultimately afford 1.4 g. of 4-chloro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline in the form of a brownish-colored solid.

c) Preparation of 4-diethylamino-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 700 mg. (0.0025 mole) of 4-chloro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline (prepared as described above) and 560 mg. (0.0075 mole) of diethylamine (0.8 ml.) in 10 ml. of N,N-dimethylformamide was stirred at room temperature overnight and then poured over ice. The resulting mixture was then filtered and the recovered solid product washed with water and then dissolved in ethyl acetate. The latter organic solution was next washed with saturated brine and dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was ultimately obtained a light yellow solid which after recrystallization from diethyl ether gave pure 4-diethylamino-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline. The yield of the first crop melting at 155—157°C. amounted to 260 mg. (34%), while the yield of the second crop melting at 153—156°C amounted to 170 mg. (22%).

Anal. Calcd. for $C_{14}H_{14}F_3N_5$: C, 54.37; H, 4.56; N, 22.64.
Found: C, 54.08; H, 4.47; N, 23.32.

Example 28

4-Isopropylamino-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 700 mg. (0.0025 mole) of 4-chloro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline (the product of Example 27b) and 443 mg. (0.0075 mole) of isopropylamine (0.64 ml.) in 10 ml. of N,N-dimethylformamide was stirred at room temperature overnight and then poured over ice. The resulting mixture was then filtered and the recovered solid product washed with water and then dissolved in diethyl ether. The latter ethereal solution was next washed with saturated brine and dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was ultimately obtained a white solid powder which after one recrystallization from diethyl ether yielded 550 mg. (74%) of pure 4-isopropylamino-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 185—187°C.

Anal. Calcd. for $C_{13}H_{12}F_3N_5$: C, 52.88; H, 4.10; N, 23.72.
Found: C, 52.73; H, 4.00; N, 23.67.

Example 29

1-Ethyl-4-(N-ethylacetylamino)-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 241 mg. (0.001 mole) of 1-ethyl-4-ethylamino-[1,2,4]triazolo[4,3-a]quinoxaline (the product of Example 17) and 2.5 g. (0.025 mole) of acetic anhydride (2.5 ml.) contained in a flame-dried reaction flask was refluxed (140°C.) under a dry nitrogen atmosphere for a period of three hours and then allowed to cool to room temperature. At this point, a precipitate formed and the resulting reaction mixture was poured into water and then extracted with chloroform. The chloroform extracts were combined, washed with water and subsequently dried over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was obtained a solid product which after one recrystallization from chloroform/diethyl ether afforded 160 mg. (57%) of 1-ethyl-4-(N-ethylacetylamino)-1,2,4-triazolo[4.3-a]quinoxaline, m.p. 185—187°C.

Anal. Calcd. for $C_{15}H_{17}N_5O$: C, 63.59; H, 6.05; N, 24.72.
Found: C, 63.17; H, 6.05; N, 24.39.

Example 30

4-Acetylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 533 mg. (0.0025 mole) of 4-amino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline (the product of Example 14) and 1.0 g. (0.01 mole) of acetic anhydride (1.0 ml.) in 20 ml. of methylene chloride was refluxed overnight (~16 hours) and then allowed to cool to room temperature. The resulting clear solution was then concentrated *in vacuo* to afford a white solid substance that was subsequently recrystallized from chloroform/diethyl ether to yield 520 mg. (82%) of pure 4-acetylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 193—195°C.

Anal. Calcd. For $C_{13}H_{13}N_5O$: C, 61.16; H, 5.13; N, 27.43.
Found: C, 60.90; H, 5.26; N, 27.66.

Example 31

4-Diacetylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 5.5 g. (0.0258 mole) of 4-amino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline (the product of Example 14) and 25 g. (0.25 mole) of acetic anhydride (25 ml.) in 60 ml. of pyridine containing 100 mg. of *p*-dimethylaminopyridine was stirred at room temperature overnight (~18 hours). The resulting slurry was then filtered to remove the insolubles and the orange-red filtrate was thereafter evaporated under a high vacuum to give a dark gummy residue. Upon the addition of water, pinkish-white crystals were obtained and these were subsequently collected by means of suction filtration, washed with a

copious amount of water and dried *in vacuo* at 50°C. to ultimately afford 2.9 g. (38%) of 4-diacetylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 157—159°C. Recrystallization of the latter material from ethyl acetate/diethyl ether then gave an analytically pure sample (m.p. 158—160°C). The pure product was further characterized by means of mass spectroscopy and nuclear magnetic resonance data, in addition to elemental analysis.

Mass spectrum: m/e, 297(P).

Anal. Calcd. for $C_{15}H_{15}N_5O_2$: C, 60.59; H, 5.09, N, 23.56.
Found: C, 60.33; H, 5.09; N, 23.41.

Example 32

The following [1,2,4]triazolo[4,3-a]quinoxaline-4-amine derivatives were prepared by employing the procedures described in the previous preparations and examples, starting from readily available materials in each instance:

7,8-dibromo-4-diethylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 199—201°C.
8-chloro-4-isopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 177—181°C.
4-ethylamino-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 223—225°C.
1-ethyl-4-ethylamino-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 234—237°C.
4-diethylamino-8-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 124—126°C.
8-chloro-1-ethyl-4-isopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 189—191°C.
4-(N-piperazino)-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 160—162°C.
8-chloro-4-(N-piperazino)-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 253—256°C.
8-chloro-4-(N-isopropylacetylamino)-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 148—151°C.
4-acetylamino-8-chloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 203—205°C.
8-chloro-1-ethyl-4-(N-isopropylacetylamino)-1,2,4-triazolo[4,3-a]quinoxaline, m.p. 155—158°C.
7,8-dichloro-4-(N-isopropylacetylamino)-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 207—210°C.
4-amino-7,8-dichloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. >260°C.
4-amino-8-chloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 248—253°C.
4-acetylamino-7,8-dichloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 230—232°C.
8-fluoro-4-isopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline m.p. 215—217°C.
4-ethylamino-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 239—242°C.
1-ethyl-8-fluoro-4-isopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 209—212°C.
7,8-difluoro-4-isopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 218—221°C.
1-ethyl-4-ethylamino-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 231—233°C.
7,8-difluoro-4-ethylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 208—211°C.
4-diethylamino-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 151—153°C.
4-diethylamino-1-ethyl-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 94—97°C.
7-chloro-4-dimethylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate (mesylate), m.p. 214—217°C.
7-chloro-4-diethylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 172—175°C.
7,8-dichloro-1-ethyl-4-(N-piperazino)-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 252—255°C.
7,8-dichloro-4-dimethylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 168—171°C.
7,8-dichloro-4-dimethylamino-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 216—219°C.
4-acetylamino-1-ethyl-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 203—205°C.
4-amino-7-chloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 240—243°C.
7-chloro-1-ethyl-4-ethylamino-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 187—189°C.
7-chloro-4-diethylamino-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 205—207°C.
4-diethylamino-7,8-difluoro-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 220—223°C.
4-acetylamino-7-chloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 210—212°C.
8-chloro-1-ethyl-4-ethylamino-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 235—238°C.
4-amino-7-chloro-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 279—282°C.
4-amino-8-chloro-1-methyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 213—215°C.
8-chloro-4-isopropylamino-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 183—185°C.
8-chloro-4-diethylamino-1-methyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 172—175°C.
4-diacetylamino-[1,2,4]triazolo[4,3-a]quinoxaline, 211—214°C.
4-diacetylamino-8-chloro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 208—210°C.
8-chloro-4-isopropylamino-1-methyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 206—208°C.
4-acetylamino-1-methyl-8-chloro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 262—264°C.
8-chloro-1-ethyl-4-trimethylacetylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 211—213°C.

7,8-difluoro-1-ethyl-4-isopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 151—152°C.

4-n-butyrylamino-8-chloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 185—187°C.

8-chloro-4-diethylamino-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline hydrate, m.p. 135—136°C.

4-amino-8-chloro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 259—261°C.

4-ethylamino-8-fluoro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 180—183°C.

8-fluoro-4-isopropylamino-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 185—188°C.

4-diethylamino-7,8-difluoro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 109—111°C.

1-ethyl-4-ethylamino-7-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 215—219°C.

4-amino-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 262—264°C.

8-chloro-4-isopropylamino-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 183—186°C.

8-chloro-4-ethylamino-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 254—256°C.

7-fluoro-4-isopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 214—216°C.

4-ethylamino-7-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 216—218°C.

4-diethylamino-8-fluoro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 146—149°C.

7,8-dichloro-1-ethyl-4-isopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 197—198°C.

8-chloro-4-diethylamino-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 194—195°C.

4-acetylamino-1-ethyl-7-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 273—275°C.

4-acetylamino-8-chloro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 215—216°C.

4-amino-8-chloro-1-phenyl-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 273—275°C.

8-chloro-4-ethylamino-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 228—230°C.

1-ethyl-7-fluoro-4-isopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 178—181°C.

4-amino-8-fluoro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline hydrate, m.p. 260—263°C.

8-chloro-1-ethyl-4R-phenylisopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 155—157°C.

4-amino-1-ethyl-7-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 285—289°C.

4-amino-1-ethyl-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 255—258°C.

4-acetylamino-8-fluoro-1-trifluoromethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 217—219°C.

4-acetylamino-1-ethyl-7-methoxy-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 202—205°C.

8-chloro-1-ethyl-4S-phenylisopropylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 156—157°C.

4-acetylamino-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 240—242°C.

4-acetylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 269—272°C.

4-amino-7-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 246—248°C.

4-amino-8-fluoro-[1,2,4]triazolo[4,3-a]quinoxaline methanesulfonate, m.p. 176—178°C.

8-chloro-4-isopropylamino-1-pentafluoroethyl-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 171—174°C.

Example 33

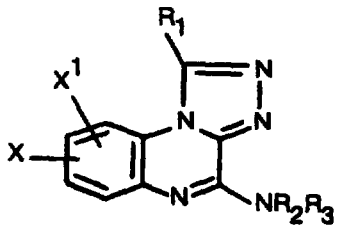
8-Chloro-1-ethyl-4-propionylamino-[1,2,4]triazolo[4,3-a]quinoxaline

A mixture consisting of 1.25 g. (0.005 mole) of 4-amino-8-chloro-1-ethyl-[1,2,4]triazolo[4,3-a]quinoxaline (m.p. 248—253°C.), a product reported in Example 32, and 15 ml. of propionic anhydride was refluxed overnight for a period of approximately 16 hours and then cooled to room temperature (~20°C.). Upon completion of this step, the resulting reaction mixture was filtered and the recovered precipitate was subsequently dissolved in chloroform. The latter organic solution was then filtered and thereafter successively washed with water, saturated aqueous sodium bicarbonate solution and saturated brine, followed by drying over anhydrous magnesium sulfate. After removal of the drying agent by means of filtration and the solvent by means of evaporation under reduced pressure, there was obtained a residual material that was subsequently chromatographed on a 150 ml. silica gel column and then eluted with chloroform/methanol (95:5 by volume). Like fractions containing the product were combined and thereafter concentrated *in vacuo* to yield a crystalline material, which was later recrystallized from chloroform/ethyl ether to ultimately afford 540 mg. (36%) of pure 8-chloro-1-ethyl-4-propionylamino-[1,2,4]triazolo[4,3-a]quinoxaline, m.p. 212—215°C.

Anal. Calcd. for $C_{14}H_{14}ClN_5O$: C, 55.36; H, 4.64; N, 23.06.
Found: C, 54.91; H, 4.59; N, 22.76.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound selected from the group consisting of [1,2,4]triazolo[4,3-a]quinoxaline-4-amine bases of the formula:



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein

X and X^1 are each selected from the group consisting of hydrogen, fluorine, chlorine, bromine and methoxy;

R_1 is selected from the group consisting of hydrogen, C_1—C_4 alkyl, C_1—C_4 perfluoroalkyl and phenyl; and

R_2 and R_3 are each selected from the group consisting of hydrogen, C_1—C_4 alkyl, phenylalkyl having up to three carbon atoms in the alkyl moiety and alkanoyl having from two to five carbon atoms, provided that at least one of R_2 and R_3 is always other than hydrogen when X and X^1 are each hydrogen and R_1 is hydrogen or methyl; or

R_2 and R_3, when taken together, complete a piperazino ring.

2. A compound as claimed in claim 1 wherein X and X^1 are each hydrogen, R_1 is hydrogen, and R_2 and R_3 are each C_1—C_4 alkyl.

3. A compound as claimed in claim 1 wherein X and X^1 are each hydrogen, R_1 is ethyl and R_3 is C_1—C_4 alkyl.

4. A compound as claimed in claim 3 wherein R_2 is hydrogen and R_3 is ethyl.

5. A compound as claimed in claim 1 wherein X and X^1 are each hydrogen, R_1 is C_1—C_4 alkyl and R_3 is acetyl.

6. A compound as claimed in claim 1 wherein at least one of X and X^1 is fluorine, R_1 and R_2 are each hydrogen and R_3 is C_1—C_4 alkyl.

7. A compound as claimed in claim 1 wherein at least one of X and X^1 is chlorine, R_1 is C_1—C_4 alkyl or trifluoromethyl, R_2 is hydrogen and R_3 is hydrogen, C_1—C_4 alkyl or alkanoyl having two to five carbon atoms.

8. A compound as claimed in claim 1 wherein at least one of X and X^1 is fluorine, R_1 is trifluoromethyl, R_2 is hydrogen and R_3 is hydrogen, C_1—C_4 alkyl or alkanoyl having from two to five carbon atoms.

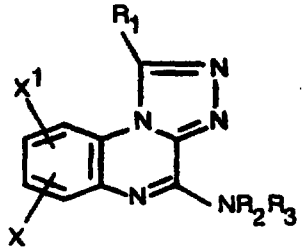
9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antidepressant/antifatigue effective amount of a compound as claimed in claim 1.

10. A pharmaceutical composition as claimed in claim 9 wherein the compound is 1-ethyl-4-ethylamino-[1,2,4]triazolo[4,3-a]quinoxaline.

11. A compound as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable acid addition salt thereof, for use as an antidepressant or antifatigue agent.

Claims for the Contracting State: AT

1. A process for preparing a [1,2,4]triazolo[4,3-a]quinoxaline-4-amine derivative of the formula:

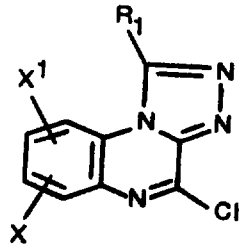


(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein X and X^1 are each selected from the group consisting of hydrogen, fluorine, chlorine, bromine and methoxy; R_1 is selected from the group consisting of hydrogen, C_1—C_4 alkyl, C_1—C_4 perfluoroalkyl and phenyl; and R_2 and R_3 are each selected from the group consisting of hydrogen, C_1—C_4 alkyl, phenylalkyl having up to three carbon atoms in the alkyl moiety and alkanoyl having from two to five carbon atoms, provided that at least one of R_2 and R_3 is always other than hydrogen when X and X^1 are each hydrogen and R_1 is hydrogen or methyl; or R_2 and R_3,

* C L M S *

when taken together, complete a piperazino ring, characterized in that a corresponding 4-chloro compound of the formula:



(IIA or IIB)

wherein X, X^1 and R^1 are each as previously defined, is reacted with an amine of the formula HNR_2R_3 wherein R_2 and R_3 are each as previously defined except that they are other than alkanoyl to form the corresponding 4-amino compound and, when required, reacting the 4-amino compound thus obtained wherein at least one of R_2 and R_3 is hydrogen with an appropriate alkanoic acid anhydride to yield the desired 4-amine derivative having the requisite alkanoyl moiety; and, if desired, converting a compound of formula (I) to a pharmaceutically acceptable acid addition salt thereof.

2. A process as claimed in claim 1 wherein the amination reaction is carried out by using an excess molar amount of amine of formula HNR_2R_3 in a reaction-inert organic solvent.

3. A process as claimed in claim 2 wherein the reaction-inert organic solvent is dimethylformamide.

4. A process as claimed in claim 2 wherein the amination reaction is conducted at a temperature of from about 0°C. to about 60°C. for a period of about two to about 24 hours.

5. A process as claimed in claim 1 wherein the acylation of the 4-amino compound is carried out under substantially anhydrous conditions using at least an equimolar amount of the appropriate alkanoic acid anhydride.

6. A process as claimed in claim 5 wherein the molar ratio of the acid anhydride to the 4-amino starting material is in the range of from about 1:1 to about 25:1, respectively.

7. A process as claimed in claim 1 wherein the acylation of the 4-amino compound is conducted at a temperature ranging from about 20°C. up to about 140°C. for a period of about one-half to about 24 hours.

8. A process as claimed in claim 1 wherein the acylation of the 4-amino compound is carried out in the presence of a neutral, reaction-inert anhydrous organic solvent.

9. A process as claimed in claim 8 wherein the neutral, reaction-inert anhydrous organic solvent is a halogenated hydrocarbon solvent.

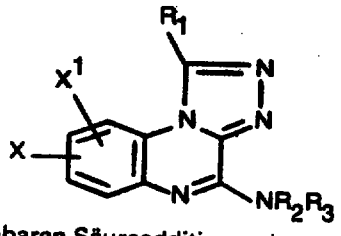
10. The process as claimed in claim 1 wherein the [1,2,4]triazolo[4,3-a]quinoxaline-4-amine derivative prepared is 1-ethyl-4-ethylamino-[1,2,4]triazolo[4,3-a]quinoxaline.

11. A process for preparing a pharmaceutical composition, comprising mixing a compound of the formula (I) as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof, with a pharmaceutically acceptable diluent or carrier.

12. A process for preparing a pharmaceutical composition comprising preparing a compound of the formula (I) or a pharmaceutically acceptable acid addition salt thereof by a process as claimed in any one of claims 1 to 10, followed by mixing the thus-produced product with a pharmaceutically acceptable diluent or carrier.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung ausgewählt aus der Gruppe, die aus [1,2,4]Triazolo[4,3-a]chinoxalin-4-amin-Basen der Formel:



(I)

und den pharmazeutisch annehmbaren Säureadditionssalzen davon besteht, worin X und X^1 jeweils unter Wasserstoff, Fluor, Chlor, Brom und Methoxy ausgewählt sind, R_1 unter Wasserstoff, (C_1—C_4)-Alkyl, (C_1—C_4)-Perfluoralkyl und Phenyl ausgewählt ist und R_2 und R_3 jeweils unter Wasserstoff, (C_1—C_4)-Alkyl, Phenylalkyl mit bis zu drei Kohlenstoffatomen im Alkylrest und Alkanoyl mit zwei bis fünf Kohlenstoffatomen ausgewählt sind, mit der Maßgabe, daß wenigstens einer der Reste R_2 und R_3 stets eine andere Bedeutung als Wasserstoff hat, wenn X und X^1 jeweils Wasserstoff sind und R_1 Wasserstoff oder Methyl ist oder R_2 und R_3 zusammengenommen einen Piperazinoring vervollständigen.

* C L M S *

4. Verfahren nach Anspruch 2, worin die Aminierungsreaktion bei einer Temperatur von etwa 0 bis etwa 60°C für etwa 2 bis etwa 24 h durchgeführt wird.

5. Verfahren nach Anspruch 1, worin die Acylierung der 4-Amino-Verbindung unter praktisch wasserfreien Bedingungen unter Verwendung von wenigstens einer äquimolaren Menge des geeigneten Alkansäureanhydrids durchgeführt wird.

6. Verfahren nach Anspruch 5, worin das Molverhältnis des Säureanhydrids zum 4-Amino-Ausgangsmaterial im Bereich von etwa 1:1 bis etwa 25:1 liegt.

7. Verfahren nach Anspruch 1, worin die Acylierung der 4-Amino-Verbindung bei einer Temperatur im Bereich von etwa 20 bis etwa 140°C für etwa 0,5 bis etwa 24 h durchgeführt wird.

8. Verfahren nach Anspruch 1, worin die Acylierung der 4-Amino-Verbindung in Gegenwart eines neutralen, reaktionsinerten, wasserfreien organischen Lösungsmittels durchgeführt wird.

9. Verfahren nach Anspruch 8, worin das neutrale, reaktionsinerte, wasserfreie organische Lösungsmittel ein halogenierter Kohlenwasserstoff ist.

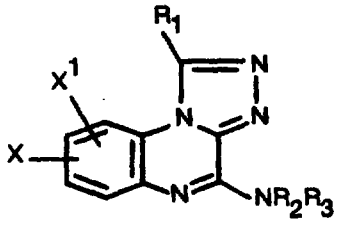
10. Verfahren nach Anspruch 1, worin das hergestellte [1,2,4]Triazolo[4,3-a]chinoxalin-4-amin-Derivat 1-Ethyl-4-ethylamino-[1,2,4]triazolo[4,3-a]chinoxalin ist.

11. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, das das Zusammenbringen einer Verbindung der Formel (I), wie in Anspruch 1 definiert, oder eines pharmazeutisch annehmbaren Säureadditionssalzes davon mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger umfaßt.

12. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, das das Herstellen einer Verbindung der Formel (I) oder eines pharmazeutisch annehmbaren Säureadditionssalzes davon nach einem Verfahren gemäß einem der Ansprüche 1 bis 10, gefolgt vom Zusammenbringen des so hergestellten Produkts mit einen pharmazeutisch annehmbaren Verdünnungsmittel oder Träger umfaßt.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composé choisi dans le groupe comprenant des [1,2,4]triazolo[4,3-a]quinoxaline-4-amines de formule:



(I)

et leurs sels d'addition d'acides pharmaceutiquement acceptables, formule dans laquelle

X et X^1 sont choisis tous deux dans le groupe comprenant l'hydrogène, le fluor, le chlore, le brome et le radical méthoxy;

R_1 est choisi dans le groupe comprenant l'hydrogène, un radical alkyle en C_1 à C_4, perfluoralkyle en C_1 à C_4 et le radical phényle; et

R_2 et R_3 sont tous deux choisis dans le groupe comprenant l'hydrogène, un radical alkyle en C_1 à C_4, phénylalkyle ayant jusqu'à 3 atomes de carbone dans la portion alkyle, et alcanoyle ayant 2 à 5 atomes de carbone, sous réserve qu'au moins l'un de R_2 et R_3 soit toujours autre chose que de l'hydrogène lorsque X et X^1 sont chacun un atome d'hydrogène et R_1 est l'hydrogène ou le radical méthyle; ou bien

R_2 et R_3, pris ensemble, complètent un noyau pipérazino.

2. Composé suivant la revendication 1, dans lequel X et X^1 sont chacun un atome d'hydrogène, R_1 est un atome d'hydrogène et R_2 et R_3 sont chacun un radical alkyle en C_1 à C_4.

3. Composé suivant la revendication 1, dans lequel X et X^1 sont chacun un atome d'hydrogène, R_1 est le radical éthyle et R_3 est un radical alkyle en C_1 à C_4.

4. Composé suivant la revendication 3, dans lequel R_2 est l'hydrogène et R_3 est le radical éthyle.

5. Composé suivant la revendication 1, dans lequel X et X^1 sont chacun un atome d'hydrogène, R_1 est un radical alkyle en C_1 à C_4 et R_3 est le radical acétyle.

6. Composé suivant la revendication 1, dans lequel au moins l'un de X et X^1 est le fluor, R_1 et R_2 sont chacun un atome d'hydrogène et R_3 est un radical alkyle en C_1 à C_4.

7. Composé suivant la revendication 1, dans lequel l'un au moins de X et X^1 est le chlore, R_1 est un radical alkyle en C_1 à C_4 ou le radical trifluorométhyle, R_2 est l'hydrogène et R_3 est l'hydrogène, un radical alkyle en C_1 à C_4 ou un radical alcanoyle ayant 2 à 5 atomes de carbone.

8. Composé suivant la revendication 1, dans lequel l'un au moins de X et X^1 est le fluor, R_1 est le radical trifluorométhyle, R_2 est l'hydrogène et R_3 est l'hydrogène, un radical alkyle en C_1 à C_4 ou un radical alcanoyle ayant 2 à 5 atomes de carbone.

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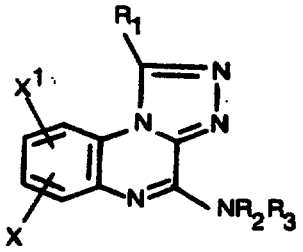
9. Composition pharmaceutique comprenant un support pharmaceutiquement acceptable et une quantité à effet antidépresseur/antifatigue d'un composé suivant la revendication 1.

10. Composition pharmaceutique suivant la revendication 9, dans laquelle le composé est la 1-éthyl-4-éthylamino[1,2,4]-triazolo[4,3-a]quinoxaline.

11. Composé suivant l'une quelconque des revendications 1 à 8 ou un sel d'addition d'acide pharmaceutiquement acceptable de ce composé, destiné à être utilisé comme agent antidépresseur ou antifatigue.

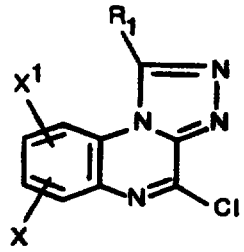
Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un dérivé de [1,2,4]triazole[4,3-a]quinoxaline-4-amine de formule:



(I)

et des sels d'addition d'acides pharmaceutiquement acceptables de ce dérivé, formule dans laquelle X et X^1 sont choisis tous deux dans le groupe comprenant l'hydrogène, le fluor, le chlore, le brome et le radical méthoxy; R_1 est choisi dans le groupe comprenant l'hydrogène, un radical alkyle en C_1 à C_4, perfluoralkyle en C_1 à C_4 et le radical phényle; et R_2 et R_3 sont tous deux choisis dans le groupe comprenant l'hydrogène, un radical alkyle en C_1 à C_4, phénylalkyle ayant jusqu'à 3 atomes de carbone dans la portion alkyle, et alcanoyle ayant 2 à 5 atomes de carbone, sous réserve qu'au moins l'un de R_2 et R_3 soit toujours autre chose que de l'hydrogène lorsque X et X^1 sont chacun un atome d'hydrogène et R_1 est l'hydrogène ou le radical méthyle; ou bien R_2 et R_3, pris ensemble, complètent un noyau pipérazino, caractérisé en ce qu'on fait réagir un composé 4-chloré correspondant de formule:



(IIA ou IIB)

dans laquelle X, X^1 et R^1 sont chacun tels que définis ci-dessus, avec une amine de formule HNR_2R_3 dans laquelle R_2 et R_3 sont chacun tels que définis ci-dessus, excepté qu'ils représentent autre chose qu'un groupe alcanoyle, pour former le composé 4-aminé correspondant et, lorsque cela est nécessaire, à faire réagir le composé 4-aminé ainsi obtenu, dans lequel l'un au moins de R_2 et R_3 est l'hydrogène, avec un anhydride d'acide alcanoïque approprié pour obtenir le dérivé 4-aminé désiré ayant le groupement alcanoyle requis; et, le cas échéant, à transformer un composé de formule (I) en un sel d'addition d'acide pharmaceutiquement acceptable de ce composé.

2. Procédé suivant la revendication 1, dans lequel la réaction d'amination est conduite en utilisant un excès molaire d'amine de formule HNR_2R_3 dans un solvant organique inerte vis-à-vis de la réaction.

3. Procédé suivant la revendication 2, dans lequel le solvant organique inerte vis-à-vis de la réaction est le diméthylformamide.

4. Procédé suivant la revendication 2, dans lequel la réaction d'amination est conduite à une température d'environ 0 à environ 60°C pendant une période d'environ 2 à environ 24 heures.

5. Procédé suivant la revendication 1, dans lequel l'acylation du composé 4-aminé est effectuée dans des conditions principalement anhydres en utilisant une quantité au moins équimolaire de l'anhydride d'acide alcanoïque approprié.

6. Procédé suivant la revendication 5, dans lequel le rapport molaire de l'anhydride d'acide à la matière 4-aminée de départ se situe dans l'intervalle d'environ 1:1 à environ 25:1, respectivement.

7. Procédé suivant la revendication 1, dans lequel l'acylation du composé 4-aminé est conduite à une température allant d'environ 20 à environ 140°C pendant une période d'environ 0,5 à environ 24 heures.

8. Procédé suivant la revendication 1, dans lequel l'acylation du composé 4-aminé est effectuée en présence d'un solvant organique anhydre neutre inerte vis-à-vis de la réaction.

* C L M S *

9. Procédé suivant la revendication 8, dans lequel le solvant organique anhydre neutre inerte vis-à-vis de la réaction est un solvant hydrocarboné halogéné.

10. Procédé suivant la revendication 1, dans lequel le dérivé de [1,2,4]triazolo[4,3-a]quinoxaline-4-amine préparé est la 1-éthyl-4-éthylamino-[1,2,4]triazolo[4,3-a]quinoxaline.

11. Procédé de préparation d'une composition pharmaceutique, consistant à mélanger un composé de formule (I) tel que défini dans la revendication 1 ou un sel d'addition d'acide pharmaceutiquement acceptable de ce composé, avec un diluant ou support acceptable du point de vue pharmaceutique.

12. Procédé de préparation d'une composition pharmaceutique, consistant à préparer un composé de formule (I) ou un sel d'addition d'acide pharmaceutiquement acceptable de ce composé par un procédé suivant l'une quelconque des revendications 1 à 10, puis à mélanger le produit ainsi formé avec un diluant ou support acceptable du point de vue pharmaceutique.

* C L M S *