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3,814,711

10-ACETAMIDO-s-TRIAZOLO-[3,4-a]-ISOQUINOLINES

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U.S. Cl. 260—287 R 1 Claim

ABSTRACT OF THE DISCLOSURE

Novel *s*-triazolo-[3,4-*a*]-isoquinoline compounds are prepared by methods analogous to known methods and exhibit anti-aggressive activity.

BACKGROUND OF THE INVENTION

The present invention relates to the pharmaceutical field, and more particularly to methods and pharmaceutical compositions for treating mammals utilizing as active agents certain novel organic heterocyclic compounds from the class known as *s*-triazolo-[3,4-*a*]-isoquinolines.

The preparation of various *s*-triazolo-[3,4-*a*]-isoquinolines is disclosed by (1) S. Naqui et al., *Indian J. Chem., 3,* 162–4 (1965); (2) G. S. Sidhu et al., *Jour. Heterocyclic Chem., 3,* 158–164 (1966); (3) J. E. Francis, U.S. Pat. 3,354,164 (1967); (4) H. K. Reimlinger et al., French Pat. 1,573,135 (1969) and (5) H. K. Reimlinger et al., *Chem. Ber.* 103, 1960–1981 (1970).

No pharmaceutical compositions or utility are disclosed in references (1), (2), (4) and (5) cited above. Francis (3) discloses that unsubstituted *s*-triazolo-[3,4-*a*]-isoquinoline and its 3-lower alkyl derivatives are coronary vasodilators.

The invention is particularly concerned with certain novel compounds useful in selectively inhibiting aggressive behavior in mammals.

It is known that certain compounds exhibit a type of central nervous system activity characterized as anti-aggressive activity. For example, it has been previously reported that benzquinamide, a central nervous system depressant (Merck Index, Eighth Ed., p. 136), and tetrabenazine, an antipsychotic agent (Merck Index, Eighth Ed., p. 1022) possess some degree of antiaggressive activity.

It has been confirmed that lesions in the septal region of the forebrain in rats produces a striking increase in emotional behavior. Brady et al., J. Comp. Physiol. Psychol. *46,* 339 (1953) and Brady et al., J. Comp. Physiol, Psychol. *48,* 412 (1955). This is accompanied by violent attack behavior in response to previously neutral stimuli ("septal rats"). The effects of depressant compounds on this type of aggressive behavior have been reported, e.g., Hunt, N.Y. Acad. Sci., *67,* 712 (1957), Randall et al., J. Pharmacol. exp. Ther. *129,* 163 (1960) and Malick et al., Arch. int. Pharmacodyn. *181,* 459 (1969). In addition, it has been shown (Karli, C. R. Soc. Biol. *149,* 2227 (1955) and Karli, Behaviour, *10,* 81 (1956)) that certain rats will readily attack and kill mice upon presentation ("killer rats"). Here again, it has been demonstrated that certain antidepressants, stimulants and anti-histaminics selectively inhibit the muricidal (mouse killing) response in these rats (Horovitz et al., Life Sci. *4,* 1909 (1965) and Horovitz et al., Int. J. Neuropharmacol. *5,* 405 (1966)). So-called "septal rats" and "killer rats" procedures have thus been established to determine the inhibitory effect of test compounds on aggressive behavior (cf. Goldberg, Arch. int. Pharmacodyn., *186,* 287 (1970).

SUMMARY OF THE INVENTION

Among the several objects of the invention may be noted the provision of certain novel *s*-triazolo-[3,4-*a*]-isoquinolines; the provision of such compounds which exhibit anti-aggressive activity; and the provision of pharmaceutical compositions and methods for inhibiting aggressive behavior in a susceptible mammal, which compositions and methods utilize the novel *s*-triazolo-[3,4-*a*]-isoquinolines as active agents. Other objects will be in part apparent and in part pointed out hereinafter.

The present invention is thus directed to novel *s*-triazolo-[3,4-*a*]-isoquinoline compounds from the group hereinafter specifically set forth. The invention is also directed to a method of inhibiting aggressive behavior in a susceptible mammal by administering to said mammal an effective amount of such an *s*-triazolo-[3,4-*a*]-isoquinoline compound and to pharmaceutical compositions comprising such a compound and a pharmaceutical carrier.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, it has now been found that certain novel *s*-triazolo-[3,4-*a*]-isoquinoline compounds exhibit anti-aggressive activity. The type and degree of anti-aggressive activity observed with *s*-triazolo-[3,4-*a*]-isoquinoline compounds is selective in nature and the presence or absence of such activity, and its degree when present, appears to be quite sensitive to the position and type of substitution on the basic *s*-triazolo-[3,4-*a*]-isoquinoline structure.

The novel *s*-triazolo-[3,4-*a*]-isoquinoline compounds of the invention which have been found to possess anti-aggressive activity are:

6-chloro-10-acetamido-*s*-triazolo-[3,4-*a*]-isoquinoline
3,6-dimethyl-*s*-triazolo-[3,4-*a*]-isoquinoline
3-methyl-7,8,9-trimethoxy-*s*-triazolo-[3,4-*a*]-isoquinoline
7,8,9-trimethoxy-*s*-triazolo-[3,4-*a*]-isoquinoline
9-methyl-*s*-triazolo-[3,4-*a*]-isoquinoline
3-methyl-5-butyl-*s*-triazolo-[3,4-*a*]-isoquinoline
5-butyl-*s*-triazolo-[3,4-*a*]-isoquinoline
3-(N-pyrrolidinyl)-9-methyl-*s*-triazolo-[3,4-*a*]-isoquinoline
3-isobutyl-5,6-dihydro-*s*-triazolo-[3,4-*a*]-isoquinoline
3-(N-pyrrolidinylmethyl)-5,6-dihydro-*s*-triazolo-[3,4-*a*]-isoquinoline

and the pharmaceutically acceptible, nontoxic acid addition salts thereof. Such addition salts may be derived from hydrochloric acid, hydrobromic acid, phosphoric acid, methanesulfonic acid and the like.

In general, the novel *s*-triazolo-[3,4-*a*]-isoquinoline compounds of the invention may be prepared by the reaction of 1-hydrazinoisoquinoline with an acidic reagent as disclosed in H. K. Reimlinger et al. French Pat. 1,573,135 (1969), either in the presence or absence of a solvent. As illustrated by the working examples hereinafter, many of the *s*-triazolo-[3,4-*a*]-isoquinolines of the invention may be prepared directly from the corresponding ring-substituted hydrazinoisoquinoline and the specific acidic agent. In the case of the two 5,6-dihydro-*s*-triazolo-[3,4-*a*]-isoquinoline compounds of the invention, these may be prepared by electrolytic or catalytic hydrogenation.

In further accordance with the invention, pharmaceutical compositions and methods useful in inhibiting aggressive behavior in susceptible mammals are provided the compositions comprising an aforementioned *s*-triazolo-[3,4-*a*]-isoquinoline compound and a pharmaceutical carrier which may be either liquid or solid material. These compositions may be administered orally or parenterally in the usual pharmaceutical forms including capsules, tablets, solutions, suspensions and the like. For example,

the *s*-triazolo-[3,4-*a*]-isoquinoline compound may be formulated with carriers such as magnesium stearate and lactose and filled into gelatin capsules. Examples of other solid pharmaceutical carriers, such as fillers, binders and lubricants, include dibasic calcium phosphate, calcium sulfate dihydrate, microcrystalline cellulose, calcium carbonate and talc. The pharmaceutical compositions of the invention may also be in the form of sterile parenteral solutions with the *s*-triazolo-[3,4-*a*]-isoquinoline compound dissolved in a sterile parenteral solvent such as polyethylene glycol, propylene glycol, water or mixtures of solvents or the compositions may be in the form of suspensions.

Where the *s*-triazolo-[3,4-*a*]-isoquinoline compound is water-insoluble, it is preferred that the compound be formulated into the pharmaceutical compositions of the invention in a micronized form, as by milling the compound by conventional methods. More particularly, it is preferred that the compound be micronized to a particle size of approximately 1–10 microns.

The following examples illustrate the invention.

In each of Examples 1–10, the indicated structure was confirmed by infrared spectroscopy.

EXAMPLE 1

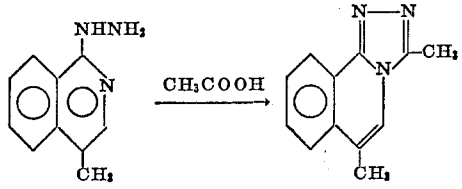
Preparation of 6-chloro-10-acetamido-*s*-triazolo[3,4-*a*]-isoquinoline

A solution of 8-acetamido-4-chloro-1-hydrazinoisoquinoline in ethyl orthoformate and formic acid was heated at reflux for 3 hours. After removal of the solvent *in vacuo*, the residue was dissolved in methanol and was treated with decolorizing carbon. The filtered solution was cooled to provide the product, M.P. 202° C.

Calculated for $C_{12}H_9ClN_4O$: C, 55.3; H, 3.46; N, 21.5; O, 6.15. Found: C, 55.6; H, 3.76; N, 21.51; O, 6.23.

EXAMPLE 2

Preparation of 3,6-dimethyl-*s*-triazolo-[3,4-*a*]-isoquinoline

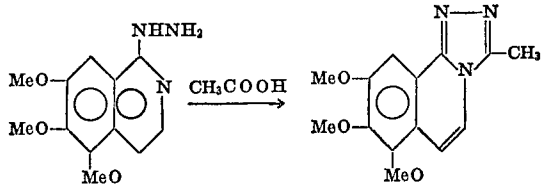


1-hydrazino-4-methylisoquinoline was dissolved in excess acetic acid and heated at reflux for 4 hours. Excess acid was removed *in vacuo* and the residue was dissolved in chloroform and washed with sodium carbonate solution. Concentration of the organic extracts and recrystallization of the residue from ethanol and cyclohexane provided the product in a yield of 62%; M.P. 213–214° C.

Calculated for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.31. Found: C, 73.12; H, 5.58; N, 21.69.

EXAMPLE 3

Preparation of 3-methyl-7,8,9-trimethoxy-*s*-triazolo-[3,4-*a*]-isoquinoline

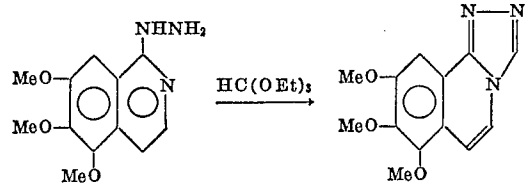


Excess acetic acid and 1-hydrazino-5,6,7-trimethoxyisoquinoline were heated at reflux for 4 hours. Excess acid was removed *in vacuo* and the residue was dissolved in dichloromethane and washed with sodium carbonate solution. Concentration of the organic layer and recrystallization from toluene provided the product in a yield of 60%; M.P. 196–198° C.

Calculated for $C_{14}H_{15}N_3O_3$: C, 61.50; H, 5.50; N, 15.40. Found: C, 61.65; H, 5.56; N, 15.32.

EXAMPLE 4

Preparation of 7,8,9-trimethoxy-*s*-triazolo-[3,4-*a*]-isoquinoline

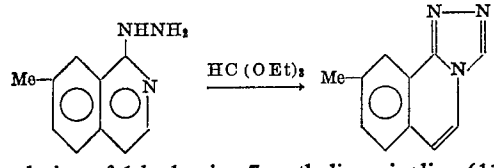


To a solution of 1-hydrazino-5,6,7-trimethoxyisoquinoline in excess triethyl orthoformate and toluene was added a catalytic amount of acetic acid and the mixture was allowed to reflux for 4 hours. The solution was concentrated, the residue was washed with sodium bicarbonate and was recrystallized from benzene to provide the product in a yield of 59%; M.P. 183–185° C.

Calculated for $C_{13}H_{13}N_3O_3$: C, 60.30; H, 5.02; N, 16.20. Found: C, 60.45; H, 5.05; N, 16.00.

EXAMPLE 5

Preparation of 9-methyl-*s*-triazolo-[3,4-*a*]-isoquinoline

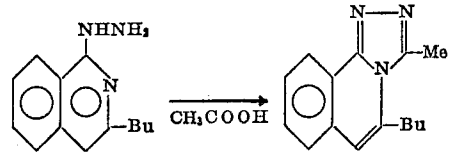


A solution of 1-hydrazino-7-methylisoquinoline (11 g.) in triethylorthoformate (70 ml.) was heated at reflux for 3 hours. After removal of the solvent, the residue was washed with sodium carbonate solution, treated with decolorizing carbon and recrystallized from toluene to provide the product in a yield of 44%; M.P. 201–202° C.

Calculated for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.05; H, 5.00; N, 22.88.

EXAMPLE 6

Preparation of 3-methyl-5-butyl-*s*-triazolo-[3,4-*a*] isoquinoline

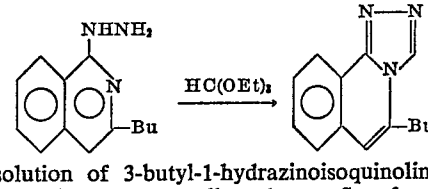


A solution of 3-butyl-1-hydrazinoisoquinoline in excess acetic acid was allowed to reflux. Removal of the excess acid, washing with sodium carbonate solution and recrystallization from cyclohexane-benzene (50/50) provided the product in a yield of 65%; M.P. 144–145° C.

Calculated for $C_{15}H_{17}N_3$: C, 75.30; H, 7.11; N, 17.55. Found: C, 75.10; H, 7.30; N, 17.95.

EXAMPLE 7

Preparation of 5-butyl-*s*-triazolo-[3,4-*a*]-isoquinoline



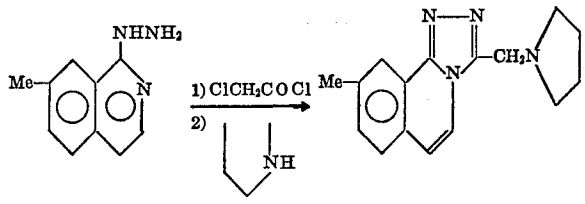
A solution of 3-butyl-1-hydrazinoisoquinoline in triethyl orthoformate was allowed to reflux for 3 hours. On cooling, the product precipitated and it was collected by filtration. Recrystallization from benzene-petroleum

ether (50/50) provided the product in a yield of 55%; M.P. 125–126° C.

Calculated for $C_{14}H_{15}N_3$: C, 74.60; H, 6.66; N, 18.65. Found: C, 74.29; H, 6.54; N, 18.85.

EXAMPLE 8

Preparation of 3-(N-pyrrolidinylmethyl)-9-methyl-*s*-triazolo-[3,4-*a*]-isoquinoline dihydrochloride

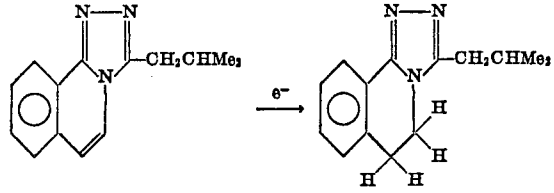


A solution of equimolar amounts of chloroacetyl chloride and 1-hydrazino-7-methylisoquinoline in nitromethane was stirred for one hour and filtered. The filter cake was heated for 8 hours with pyrrolidine and the reaction mixture was suspended in water. The aqueous suspension was extracted with dichloromethane, and the organic layer was concentrated. The concentrate was treated with methanolic hydrogen chloride and the product was recrystallized from ethanol-ether in a yield of 40%; M.P. 252–254° C.

Calculated for $C_{16}H_{18}N_4 \cdot 2HC$:1 C, 56.55; H, 5.90; N, 16.50; Cl, 20.98. Found: C, 56.31; H, 6.16; N, 16.40; Cl, 21.13.

EXAMPLE 9

Preparation of 3-isobutyl-5,6-dihydro-*s*-triazolo-[3,4-*a*]-isoquinoline

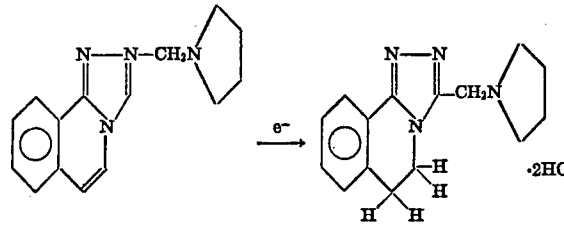


3-isobutyl-*s*-triazolo-[3,4-*a*]-isoquinoline (2.25 g., 10 mmol.), tetramethylammonium chloride (5.5 g.) and 50 ml. methanol were placed in the cathode of an electrochemical cell, and water (2 ml.), allyl alcohol (3 ml.) and methanol (20 ml.) were placed at the anode. The reduction was carried out at a constant voltage of 5 volts and the current varied from 0.1 to 0.41 amperes. On completion of the reduction, the methanolic layer was concentrated; water was added, and the solution was extracted with benzene. Evaporation of the benzene extracts provided a solid, which was recrystallized from ether to provide the product, 2.0 g. (87%) as white needles; M.P. 107–108° C.

Calculated for $C_{14}H_{17}N_3$: C, 73.97; H, 7.54; N, 18.49. Found: C, 73.92; H, 7.12; N, 18.64.

EXAMPLE 10

Preparation of 3-(N-pyrrolidinylmethyl)-*s*-triazolo-[3,4-*a*]-isoquinoline dihydrochloride



Two separate batches of 3-(N-pyrrolidinylmethyl)-*s*-triazolo-[3,4-*a*]-isoquinoline (20 mmol.), tetramethylammonium chloride (100 mmol.) in methanol were placed in the cathode of an electrochemical cell and tetramethylammonium chloride (2 g.), allyl alcohol (3 ml.) and methanol (20 ml.) were placed in the anode compartment. A voltage of 5 volts was applied and the current varied from 0.6 to 0.54 amperes. The methanolic solutions were evaporated; the residue was treated with water and the mixture was extracted into dichloromethane. The organic extracts were combined and concentrated, and the residues were dissolved in 5 ml. of carbon tetrachloride. On cooling, crystals were deposited and collected and the filtrates were chromatographed on acidic alumina followed by silica gel. The crystals and the chromatographed material were dissolved in methanol and treated with methanolic hydrogen chloride. The product was collected by filtration; M.P. (free base) 25–30° C., M.P. (dihydrochloride salt) 211–238° C. (dec.).

In the following animal studies, male hooded rats of the Long-Evans strain, weighing between 200 and 300 grams, and male albino mice, weighing approximately 20 grams, were used as subjects. They were permitted food and water *ad libitum* except during drug studies and during the period in which killer rats were selected.

EXAMPLE 11

The anti-aggressive activity of representative compounds of the invention was determined using the following "septal rats" test procedure.

Bilateral electrolytic lesioning, utilizing anodal DC current, of the septal area was performed under pentobarbital anesthesia. The animals were stereotaxically lesioned, using a slight modification of the method of Stark and Henderson (Int. H. Neuropharmacol., *5*, 385 (1966)), in which a current intensity of 7 milliamperes was delivered for 15 seconds to each septal region. All animals were given penicillin prophylactically, and were initially tested 3 to 6 days after lesioning. The Konig and Klippel atlas (cf. The Rat Brain, Williams & Wilkins Co., Baltimore, Md., 1963) was utilized for histological verification of lesion sites in selected animals. A scoring system was used which measured only the "aggressiveness" component of the septal syndrome. The animals were tail restrained and evaluated before and 60 minutes after the intraperitoneal injection (I.P.) or oral administration of the compounds tested. Two inanimate objects, a pencil and a glove, were offered and reactions were graded as: 0=indifference to either stimulus, 1=nibbling of one or both objects, 2=voracious attack of 1 object, 3=voracious attack of both objects. Only rats which exhibited a score of 3 prior to injection of a test compound were used, and animals which showed a 0 or 1 score at retest (60 minutes post injection) were considered blocked. The ED_{50} value was obtained for each compound tested and is defined as that dose which results in a score of 0 or 1 in 50% of the animals tested. The following results were obtained:

TABLE 1

Compound	Mode of administration	Anti-aggressive activity (ED_{50}), mg./kg.)
6-chloro-10-acetamido-*s*-triazolo-[3,4-*a*]-isoquinoline.	I.P.	[1] 25
3,6-dimethyl-*s*-triazolo[3,4-*a*]-isoquinoline	I.P.	17.5
3-methyl-7,8,9-trimethoxy-*s*-triazolo-[3,4-*a*]-isoquinoline.	I.P.	19.5
7,8,9-trimethoxy-*s*-triazolo[3,4-*a*]-isoquinoline	I.P.	9.8
9-methyl-*s*-triazolo-[3,4-*a*]-isoquinoline	I.P.	7.6
	Oral	17
3-(N-pyrrolidinylmethyl)-9-methyl-*s*-triazolo-[3,4-*a*]-isoquinoline hydrochloride.	I.P.	[1] 25
	Oral	[1] 30
3-isobutyl-5,6-dihydro-*s*-triazolo-[3,4-*a*]-isoquinoline.	I.P.	[1] 25
3-(N-pyrrolidinylmethyl)-5,6-dihydro-*s*-triazolo-[3,4-*a*]-isoquinoline hydrochloride	I.P.	100

[1] Approximately.

EXAMPLE 12

The anti-aggressive activity of 3,6-dimethyl-*s*-triazolo-[3,4-*a*]-isoquinoline was determined using the following "killer rats" test procedure.

The animals were housed individually for approximately 6 weeks and maintained on a restricted food intake of 15 grams per day of solid food and water *ad libitum*. After isolation, the rats were tested for their mouse-killing response and only those animals which killed mice within 2 minutes after presentation on 3 consecutive days were used. The selected animals were tested twice prior to treatment and at 30, 60, 120, 180 and 240 minutes after intraperitoneal injection of the test compound. The ED_{50} was obtained and is defined as that dose which blocks attacks in 50% of the animals tested. The ED_{50} for 3,6-dimethyl-*s*-triazolo-[3,4-*a*]-isoquinoline was found to be 29.5 mg./kg.

EXAMPLE 13

The anti-aggressive activity of 9-methyl-*s*-triazolo-[3,4-*a*]-isoquinoline was determined using the following "isolated fighting mice" procedure.

The test animals were male mice which had been isolated in a cage for three weeks. The mice were aggressive and would attack within 5 minutes a non-isolated male mouse placed in its cage. After interaction of 5 minutes, the second mouse is removed. If no fighting occurred during this interval, the isolated mouse was considered to have been rendered non-aggressive. The ED_{50} was obtained and is defined as that dose of the test compound (administered orally or by intraperitoneal injection) which renders 50% of the animals tested non-aggressive. The ED_{50} for 9-methyl-*s*-triazolo-[3,4-*a*]-isoquinoline was found to be 24.5 mg./kg. for intraperitoneal injection and 36 mg./kg. for oral administration.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

What is claimed is:

1. 6 - chloro - 10 - acetamido - *s* - triazolo-[3,4-*a*]-isoquinoline.

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Goldberg et al.: Chem. Abstr., vol. 74, col. 11704m (article dated February 1970).

DONALD G. DAUS, Primary Examiner

U.S. Cl. X.R.

204—73 R; 260—288 R; 424—258

PO-1050
(5/69)

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,814,711 Dated June 4, 1974

Inventor(s) Fernand G. F. Eloy and Morton E. Goldberg

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

The title, reading "10-Acetamido-s-Triazolo-[3,4-a]-Isoquinoles" should read -- 6-Chloro-10-Acetamido-s-Triazolo-[3,4-a]-Isoquinoline --.

Signed and sealed this 29th day of October 1974.

(SEAL)
Attest:

McCOY M. GIBSON JR.
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents