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AS-TRIAZINO[5,6-b]INDOLES

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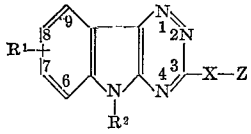
Int. Cl. C07d *57/02*; A61k *27/00*

U.S. Cl. 260—249.9 7 Claims

ABSTRACT OF THE DISCLOSURE

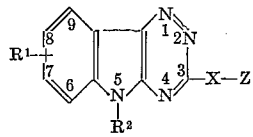
As-triazino[5,6-b]indoles of the formula:



where R^1 is hydrogen, halogen, such as chloro, bromo or fluoro; alkyl of 1–4 carbon atoms, such as methyl or ethyl; hydroxy, alkoxy of 1–4 carbon atoms, such as methoxy or ethoxy; nitro, amino, or trifluoromethyl; R^2 is hydrogen, lower alkyl of 1–4 carbon atoms, benzyl, or phenethyl; X is NR^3, wherein R^3 is hydrogen, methyl, or lower alkanoyl of 1–4 carbon atoms, such as acetyl; Z is $AlkOR^6$, where Alk is branched or straight chain alkylene of 2 to 10 carbon atoms and may be additionally substituted with an aryl, preferably phenyl, or a hydroxy group; and R^6 is lower alkyanoyl of 1–8 carbon atoms, preferably 1–4, such as acetyl or propionyl; or lower alkyl of 1–4 carbon atoms such as methyl or ethyl, exhibit antiviral activity. These compounds also include the N-oxide derivatives and acid addition salts.

This application is a continuation-in-part of Ser. No. 658,644, filed Aug. 7, 1967, which is a continuation-in-part of Ser. No. 396,727, filed Sept. 15, 1964, now abandoned.

The present invention is concerned with novel heterocyclic compounds. More particularly, the present invention is concerned with as-triazino[5,6-b]indoles of the general formula



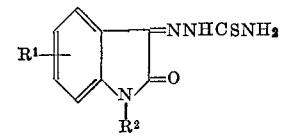
(I)

where R^1 is hydrogen, halogen, such ac chloro, bromo or fluoro; alkyl of 1–4 carbon atoms, such as methyl or ethyl; hydroxy, alkoxy of 1–4 carbon atoms, such as methoxy or ethoxy; nitro, amino, or trifluoromethyl; R^2 is hydrogen, lower alkyl of 1–4 carbon atoms, benzyl, or phenethyl; X is NR^3, wherein R^3 is hydrogen, methyl, or lower alkanoyl of 1–4 carbon atoms, such as acetyl; Z is $AlkOR^6$, where Alk is branched or straight chain alkylene of 2 to 10 carbon atoms and may be additionally substituted with an aryl, preferably phenyl, or a hydroxy group; and R^6 is lower alkanoyl of 1–8 carbon atoms, preferably 1–4, such as acetyl or propionyl; or lower alkyl of 1–4 carbon atoms, such as methyl or ethyl. N-oxide derivatives are also part of the present invention. The compounds of Formula I are bases and form acid addition salts with non-toxic acids and quaternary ammonium

salts. Such conventional pharmaceutically acceptable acid addition salts are also part of the present invention.

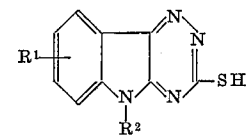
The compounds of the invention include 3-(3-acetoxypropylamino) - 5 - methyl-as-triazino[5,6-b]indole,3-[N-(3 - acetoxypropyl)acetamido] - 5 - methyl-as-triazino-[5,6-b]indole, 3-(3-methoxypropylamino) - 5 - methyl-as-triazino-[5,6-b]indole, 3-(3-acetoxy - 2 - methyl-2-phenylpropylamino) - 5 - methyl-as-triazino[5,6-b]indole, 3-(2-acetoxyethylamino) - 5 - methyl-as-triazino[5,6-b]indole, 8-chloro - 3 - (2-acetoxyethylamino) - 5 - methyl-as-triazino[5,6-b]indole, 3-(5-acetoxypentylamino)-5-methyl-as-triazino[5,6-b]indole, 3 - (6-heptanoyloxyhexylamino)-5 - methyl-as-triazino[5,6-b]indole, 3 - (4-ethoxybutylamino) - 5 - methyl-as-triazino[5,6-b]indole, 3-(3-propionoxypropylamino) - 5 - phenethyl-as-triazino[5,6-b]indole, 3-(3-methoxybutylamino) - 5 - methyl-as-triazino [5,6-b]indole, 3-(3-methoxypropylamino) - 5 - benzyl-as-triazino[5,6-b]indole, 5-ethyl-3-(3-acetoxypropylamino)-as-triazino[5,6 - b]indole, 3-(3-methoxypropylamino) - 5-propyl-as-triazino[5,6-b]indole, 3-(3-propionoxypropylamino) - 5 - methyl-as-triazino[5,6-b]indole, 3-(3-acetoxy-2,2-dimethylpropylamino) - 5 - methyl-as-triazino[5,6-b] indole, and 3 - (3-methoxy - 3 - methylbutylamino)-5-methyl-as-triazino[5,6-b]indole.

The compounds of Formula I may be prepared by the cyclization of isatin β-thiosemicarbazones of the general formula



(II)

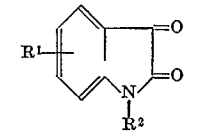
wherein R^1 and R^2 have the meanings given above, to give 3-mercapto-as-triazino[5,6-b]indoles of the general formula



(III)

and then converting the compounds of Formula III to compounds of Formula I by conventional methods. The isatins are either known, prepared by known methods, or disclosed in our copending application, Ser. No. 745,124, filed on the same day as the present application.

The thiosemicarbazones of Formula II may be cyclized to give the compounds of Formula III by, for example, refluxing in the presence of ammonia or aqueous potassium carbonate. Alternatively, the thiosemicarbazones need not be isolated in which case thiosemicarbazide and the isatin of Formula IV



(IV)

are refluxed together in aqueous potassium carbonate solution.

Compounds of Formula I may then be prepared by reacting the 3-mercapto-as-triazino[5,6-b]indole of Formula III with an aminating agent, preferably a hydroxyalkylamine, an alkoxyalkylamine, or an acyloxyalkylamine. The compound of Formula III may be heated under reflux with the aminating agent in an inert solvent such as butanol or an excess of the reacting amine may be used as the solvent. Alternatively, if the aminating

agent is a low boiling amine, an alcoholic solution of it may be heated in a sealed tube with the compounds of Formula III. The latter, in the solid state, are principally in the 3-thione (C=S) form.

The 3-acyloxyalkylaminotriazinoindoles are also produced by acylating the corresponding hydroxyalkylamino compound with an anhydride or acyl halide according to conventional procedure. Reaction for short periods of time (5–15 minutes) gives the acyloxy product, whereas treatment for longer periods (e.g. 2 hours) results additionally in acylation of the 3-nitrogen atom to give ester amides.

The hydroxyalkylaminotriazinoindoles are either known, prepared by known methods, or disclosed in copending application Ser. No. 745,124, filed on the same day as the present application.

If desired, the basic compounds of Formula I obtained by any of the processes given above may be quaternized or converted into their salts with pharmaceutically acceptable inorganic or organic acids.

For the purpose of further illustration of this invention, the following examples are set forth in detail below.

EXAMPLE 1

3-mercapto-5-methyl-as-triazino[5,6-b]indole

(a) 6.0 g. of N-methylisatin thiosemicarbazone was suspended in 1.5 l. of water containing 15 ml. of ammonia solution of sp.gr. 0.880 and the mixture was boiled under reflux for 24 hours. After cooling, a small amount of insoluble material was removed by filtration and discarded. The filtrate was evaporated under reduced pressure to about one third of its volume and, after cooling, the yellow solid which separated was filtered and recrystallized from 50% aqueous dimethyl formamide; 3-mercapto-5-methyl-as-triazino[5,6-b]indole was obtained, M.P. 279°–281° C.

The following compounds were prepared in a similar manner:

3-mercapto-as-triazino[5,6-b]indole, M.P. higher than 360° C.
3-mercapto-5-ethyl-as-triazino[5,6-b]indole, M.P. 294° C.
3-mercapto-5-propyl-as-triazino[5,6-b]indole, M.P. 278° C.

(b) 5 g. of N-methylisatin thiosemicarbazone was suspended in 100 ml. of water containing 4.4 g. of potassium carbonate and the mixture was boiled under reflux for 75 minutes. The orange colored solution was cooled, diluted with 100 ml. of water and acidified with acetic acid. The yellow solid which separated was filtered off, washed with water, dried at 100° C. and recrystallized from a large volume of methanol to give 3-mercapto-5-methyl-as-triazino[5,6-b]indole, M.P. 278°–282° C.

The following compounds were prepared in a similar manner:

3-mercapto-as-triazino[5,6-b]indole, M.P. higher than 360° C.
3-mercapto-5-methyl-8-chloro-as-triazino[5,6-b]indole, M.P. 315°–316° C.
3-mercapto-8-nitro-as-triazino[5,6-b]indole, M.P. higher than 350° C.
3-mercapto-8-methoxy-as-triazino[5,6-b]indole, M.P. 331° C.
3-mercapto-5-methyl-8-bromo-as-triazino[5,6-b]indole, M.P. higher than 350° C.
3-mercapto-5-methyl-8-nitro-as-triazino[5,6-b]indole, M.P. 283° C.

(c) 16 g. of N-methylisatin, 10 g. of thiosemicarbazide and 21 g. of potassium carbonate were boiled under reflux in 500 ml. of water for 7 hours. A small amount of insoluble material was removed by filtration and discarded and the filtrate was cooled and acidified with acetic acid. The solid which separated was filtered off, washed with water and dried at 100° C. to give 3-mercapto-5-methyl-as-triazino[5,6-b]indole, M.P. 275°–281° C.

The following compounds were prepared in a similar manner:

3-mercapto-7-methoxy-as-triazino[5,6-b]indole, M.P. 309° C.
3-mercapto-5-propyl-8-chloro-as-triazino[5,6-b]indole, M.P. 270°–275° C.

EXAMPLE 2

3-(2-hydroxyethylamino)-5-methyl-as-triazino[5,6-b]indole

5 g. of 3-mercapto-5-methyl-as-triazino[5,6-b]indole, 10 ml. of 2-hydroxyethylamine and 20 ml. of butanol were boiled under reflux for 8 hours. During this time the solid dissolved and hydrogen sulphide was evolved. On cooling, a yellow solid separated. The mixture was diluted with about 200 ml. of water and the solid was filtered off and recrystallized from 50% aqueous ethanol. The product was obtained as pale yellow needles, M.P. 235°–236° C. Acetylation with acetic anhydride as in Example 17 gives the 2-acetoxy product.

EXAMPLE 3

3-(3-hydroxypropylamino)-5-methyl-as-triazino[5,6-b]indole

A solution of 2 g. of 3-mercapto-5-methyl-as-triazino[5,6-b]indole and 20 ml. of 3-aminopropanol was refluxed for 1.5 hours, hydrogen sulphide being evolved. On cooling, the solution was poured into water and the precipitated solid was removed by filtration, washed with water and dried. Recrystallization from ethanol gave 3-(3-hydroxypropylamino)-5-methyl-as-triazino[5,6-b]indole as yellow needles, M.P. 164°–165° C.

The hydrochloride crystallized from ethanol as yellow needles, M.P. 214°–215° C.

The following compounds were prepared in a similar manner:

3-(2-hydroxyethylamino)-as-triazino[5,6-b]indole, M.P. 270°–271° C.
3-(3-hydroxypropylamino)-as-triazino[5,6-b]indole, M.P. 248°–249° C.
8-chloro-3-(2-hydroxyethylamino)-5-methyl-as-triazino [5,6-b]indole, M.P. 262°–263° C.
8-chloro-3-(3-hydroxypropylamino)-5-methyl-as-triazino [5,6-b]indole, M.P. 203°–204° C.

These products are all acrylated by the conventional procedures described derein.

EXAMPLE 4

3-(3-hydroxy-3-methylbutylamino)-5-methyl-as-triazino[5,6-b]indole

A mixture of 4.2 g. of 3-mercapto-5-methyl-as-triazino [5,6-b]indole and 6.4 g. of 4-amino-2-methyl-2-butanol was heated in a bath kept at 168°–170° C. for 45 minutes. The bath temperature was then raised to 180° and the resulting solution was stirred at 170°–180° C. for 4 hours, hydrogen sulphide being evolved. The mixture was set aside for 63 hours and the semi-solid mass was then stirred with 50 ml. of water. The undissolved solid was filtered off, washed thoroughly with water and dried at 100° C. Recrystallization from isopropanol, about 17 ml. per gm., gave 3.15 g. of the product as pale yellow rosettes, M.P. 192°–193° C.

EXAMPLE 5

3-(3-hydroxy-2,2-dimethylpropylamino)-5-methyl-as-triazino[5,6-b]indole

6 g. of 3-mercapto-5-methyl-as-triazino[5,6-b]indole in 18 g. of 3-amino-2,2-dimethylpropanol were heated with

stirring at 140°–150° C. for 12 hours until the hydrogen sulphide ceased. The suspension was cooled and poured into water, and the solid which separated was filtered off and dried at 100° C. under vacuum. Recrystallization from isopropanol gave 3.2 g. of 3-(3-hydroxy-2,2-dimethylpropylamino)-5-methyl-as-triazino[5,6-b]indole as yellow platelets, M.P. 228°–228.5° C.

EXAMPLE 6

3-(3-hydroxypropylamino)-5-phenethyl-as-triazino [5,6-b]indole

A solution of 8 g. of 3-mercapto-5-phenethyl-as-triazino [5,6-b]indole in 29 ml. of 3-aminopropanol was heated in a bath heated at 160° C. for 5 hours, hydrogen sulphide being evolved. The mixture was set aside overnight, and then added to 250 ml. of water. The solid was filtered off, washed with water and dried. Recrystallization from aqueous ethanol gave 7 g. of 3-(3-hydroxypropylamino)-5-phenethyl-as-triazino[5,6-b]indole as clusters of pale yellow needles, M.P. 154.5°–155° C.

EXAMPLE 7

3-[(1-hydroxymethyl)propylamino]-5-methyl-as-triazino[5,6-b]indole

A solution of 10 g. of 3-mercapto-5-methyl-as-triazino [5,6-b]indole in 45 ml. of 2-amino-1-butanol was heated with stirring at 160°–170° C. for 5½ hours, then cooled and poured into 300 ml. of water. A dark brown gum was salted out of solution which solidified on standing. Recrystallization from benzene gave 2.38 g. of 3-[(1-hydroxymethyl)propylamino] - 5 - methyl - as - triazino [5,6-b]indole, as buff colored rosettes, M.P. 176°–176.5° C.

EXAMPLE 8

5-ethyl-3-(3-hydroxypropylamino)-as-triazino [5,6-b]indole

A solution of 10 g. of 5-ethyl-3-mercapto-as-triazino [5,6-b]indole in 25 ml. of 3-aminopropanol was heated at 150°–160° C. for 5 hours, cooled, stirred with 100 ml. of water, and the yellow solid was filtered off, washed with water and dried to give 10 g. of 5-ethyl-3-(3-hydroxypropylamino)-as-triazino[5,6-b]indole as a yellow crystalline solid. Recrystallization of a small sample from ethanol gave pale yellow crystals, M.P. 151°–152° C.

EXAMPLE 9

3-(3-hydroxypropylamino)-5-benzyl-as-triazino [5,6-b]indole

A solution of 10 g. of 3-mercapto-5-benzyl-as-triazino [5,6-b]indole in 50 ml. of 3-amino-1-propanol was refluxed for 6 hours until the evolution of hydrogen sulphide ceased. The solution was cooled and poured into 300 ml. of water, and the solid which separated was filtered off and dried at 60° C. under vacuum. Recrystallization from ethanol gave 6.8 g. of the product as yellow needles, M.P. 186°–187° C.

EXAMPLE 10

3-(4-hydroxybutylamino)-5-methyl-as-triazino [5,6-b]indole

A solution of 10 g. of 3-mercapto-5-methyl-as-triazino [5,6-b]indole in 25 ml. of 4-aminobutanol was heated to 160°–180° C. for 1 hour and 20 minutes, and at 185°–200° C. for 4 hours, after which the evolution of hydrogen sulphide had ceased. After cooling and pouring into 200 ml. of water, crystallization began within a few minutes. The mixture was left overnight, then the crystals were filtered off, washed thoroughly with water and dried. Recrystallization from ethanol, about 5 ml. per gm., gave 7.35 g. of the product as clusters of yellowish plates, M.P. 146°–147° C.

EXAMPLE 11

3-(5-hydroxypentylamino)-5-methyl-as-triazino[5,6-b] indole

A solution of 2 g. of mercapto-5-methyl-as-triazino-[5,6-b]indole in 10 g. of 5-aminopentanol was heated to 140°–160° C. for 30 minutes, hydrogen sulphide being evolved. On cooling, the solution was poured into water and the precipitated solid was filtered off, washed with water and dried. Recrystallization from ethanol gave 3-(5 - hydroxypentylamino)-5-methyl-as-triazino[5,6-b]indole as yellow needles, M.P. 158°–158.5° C. Hydrochloride: yellow needles, M.P. 191°–192° C. (from ethanol).

The following compound was obtained in a similar manner:

3 - (6 - hydroxyhexylamino)-5-methyl-as-triazino[5,6-b] indole, M.P. 124°–125° C. Reaction of these products with heptanoyl chloride gives the heptanoyloxypentylamino and heptanoyloxyhexylamino products, respectively.

EXAMPLE 12

3-(3-hydroxypropylamino)-5-propyl-as-triazino[5,6-b] indole

A solution of 10 g. of 3-mercapto-5-propyl-as-triazino-[5,6-b]indole in 50 ml. of 3-aminopropanol was heated at 160° C. (bath temperature) for 5 hours, after which the evolution of hydrogen sulphide ceased. The mixture was poured into water and the precipitate filtered, washed with water and dried at 100° C. Recrystallization from benzene-light petroleum ether (B.P. 80°–100° C.) gave 7.6 g. of 3-(3-hydroxypropylamino)-5-propyl-as-triazinol[5,6-b]indole as pale yellow crystals, M.P. 142.5°–143.5° C.

EXAMPLE 13

3-(3-propionoxypropylamino)-5-methyl-as-triazino[5,6-b] indole

15 g. of 3-(3-hydroxypropylamino)-5-methyl-as-triazino[5,6-b]indole in 120 ml. of propionic anhydride was heated on a steam bath for 10 minutes and immediately poured into 500 ml. of water and basified with 2 N Na_2CO_3 solution. The solid product was filtered off and dried at 70° C. under vacuum. Recrystallization from ethyl methyl ketone gave 8.18 g. of the propionate as lime green needles, M.P. 158°–160° C.

EXAMPLE 14

3-(3-hydroxybutylamino)-5-methyl-as-triazino[5,6-b] indole

A solution of 5 g. of 3-mercapto-5-methyl-as-triazino-[5,6-b]indole in 8.2 g. of 4-amino-2-butanol was heated at 160°–170° C. (oil bath temperature) for 5½ hours. The solid which had separated on cooling was stirred with 80 ml. of water and the undissolved solid was filtered off, washed thoroughly with water and dried at 100° C. Recrystallization from a mixture of benzene and light petroleum ether, B.P. 80°–100° C., gave 4.05 g. of the product as clusters of pale yellow needles, M.P. 168°–168.5° C.

EXAMPLE 15

3-(3-methoxypropylamino)-5-methyl-as-triazino[5,6-b] indole

A solution of 10 g. of 3-mercapto-5-methyl-as-triazino-[5,6-b]indole in 25 ml. of 3-methoxypropylamine was refluxed for 8 hours until the evolution of hydrogen sulphide was complete. The solution was cooled and poured into water to give yellow needles. Recrystallization from ethanol gave 5.45 g. of 3-(3-methoxypropylamino)-5-methyl-as-triazino[5,6-b]indole, M.P. 140.5°–141.5° C.

EXAMPLE 16

3-(2,3-dihydroxypropylamino)-5-methyl-as-triazino [5,6-b]indole

A solution of 10 g. of 3-mercapto-5-methyl-as-triazino-[5,6-b]indole in 30 ml. of 1-amino-2,3-propanediol was heated at 170°–190° C. for 5½ hours until the hydrogen sulphide evolution had ceased. The solution was cooled, poured into methanol, the solid was filtered off, washed with methanol and dried at 50° C. under vacuum. Recrystallization from ethanol gave 5.1 g. of 3-(2,3-dihydroxypropylamino) - 5-methyl-as-triazino[5,6-b]indole as pale yellow rosettes, M.P. 194°–195° C.

EXAMPLE 17

3-(3-acetoxypropylamino)-5-methyl-as-triazino[5,6-b] indole

10 g. of 3 - (3 - hydroxypropylamino)-5-methyl-as-triazino[5,6-b]indole in 75 ml. of acetic anhydride were heated on a steam bath for 7 minutes until all the solid had dissolved. The solution was immediately poured into 500 ml. of water, and basified with 2 N sodium carbonate. The solid which separated was filtered off, washed with water, and dried at 70° C. under vacuum. Recrystallization from ethyl methyl ketone gave 5.72 g. of 3-(3-acetoxypropylamino) - 5 - methyl - as-triazino[5,6-b]indole, M.P. 185.5°–186.5° C.

EXAMPLE 18

3-[N-(3-acetoxypropyl)acetamido]-5-methyl-as-triazino [5,6-b]indole

15 g. of 3-(3-hydroxypropylamino)-5-methyl-astriazino [5,6-b]indole in 100 ml. of acetic anhydride was heated on a steam bath for 2 hours. The solution was cooled, poured into 500 ml. of water, and basified with 2 N sodium carbonate. The oil which separated was extracted with 750 ml. of chloroform, and the extract dried over $MgSO_4$, and concentrated. The crystallized product obtained on standing gave on recrystallization from a mixture of benzene and lighter petroleum B.P. 80°–100° C. petroleum ether, 7.52 g. of product as a fine white solid, M.P. 83.5°–84° C.

EXAMPLE 19

3-(3-hydroxypropylamino)-5-methyl-as-triazino[5,6-b] indole N^2-oxide

10 g. of 3 - (3 - hydroxypropylamino)-5-methyl-as-triazino[5,6-b]indole was dissolved in 100 ml. of acetic acid. 10 ml. of 100 vol. hydrogen peroxide was slowly added and the resulting solution was kept at room temperature for 4 days. At the end of this time 140 ml. of ammonium hydroxide (sp. gr.=0.88) was added, keeping the temperature below 30° C. The yellow solid that separated was filtered off, washed with water and dried at 105° C. Recrystallization from ethanol gave 1.35 g. of 3-(3-hydroxypropylamino)-5-methyl-as-triazino[5,6-b]indole N^2-oxide as small yellow crystals, M.P. 216°–218° C. (dec.).

EXAMPLE 20

3-(3-hydroxy-2-methyl-2-phenylpropylamino)-5-methyl-as-triazino[5,6-b]indole

10 g. of 3-mercapto-5-methyl-as-triazino[5,6-b]indole and 30 g. of 3-amino-2-methyl-2-phenylpropanol were heated with stirring at 170°–185° C. for 7 hours until all the hydrogen sulfide had evolved. The mixture was cooled and 85 mls. of acetone were added with scratching. The solid which separated was filtered off, washed with ether and dried at 100° C. under vacuum. Recrystallization from isopropanol gave 5.4 g. of the triazino indole as yellow needles M.P. 186.5°–188° C.

EXAMPLE 21

The following hydroxyalkylaminotriazinoindoles are acetylated with acetic anhydride as in Example 17 to give the corresponding 3-acetoxypropylaminotriazinoindole products.

3-(3-hydroxy-3-methylbutylamino)-5-methyl-8-trifluoromethyl-as-triazino[5,6-b]indole
3-(3-hydroxy-3-methylbutylamino)-5-methyl-8-fluoro-as-triazino[5,6-b]indole
3-(3-hydroxy-3-methylbutylamino)-5-methyl-8-butyl-as-triazino[5,6-b]indole

The following hydroxyalkylaminotriazinoindoles are acetylated with acetic anhydride as in Example 18 to give the corresponding 3-[N - (3 - acetoxypropyl)acetamido]triazinoindoles.

3-(3-hydroxy-3-methylbutylamino)-5-methyl-8-hydroxy-as-triazino[5,6-b]indole
3-(3-hydroxy-3-methylbutylamino)-5-methyl-8-bromo-as-triazino[5,6-b]indole
3-(3-hydroxy-3-methylbutylamino)-5-methyl-8-butyl-as-triazino-[5,6-b]indole
3-(3-hydroxy-3-methylbutylamino)-5-methyl-8-NO_2-as-triazino[5,6-b]indole
3-(3-hydroxy-3-methylbutylamino)-5-methyl-8-amino-as-triazino[5,6-b]indole

The following 3-mercaptotriazinoindoles are treated with 3-methoxypropylamine as in Example 15 to give the corresponding 3 - (3 - methoxypropylamino)triazinoindoles.

3-(3-hydroxy-3-methylbutylamino)-5-methyl-8-methoxy-as-triazino[5,6-b]indole
3-(3-hydroxy-3-methylbutylamino)-5-methyl-8-butoxy-as-triazino[5,6-b]indole
3-(3-hydroxy-3-methylbutylamino)-5,8-dimethyl-as-triazino[5,6-b]indole

The compounds of the invention exhibit antiviral activity, and are particularly active against rhinoviruses and vaccinia virus. They have been found to be effective in inhibiting the growth of various strains of rhinoviruses in the standard tube dilution test, described hereinbelow.

Tube cultures of diploid human embryonic lung (WI–26) cells were obtained from Baltimore Biological Laboratories in Eagle's Minimum Essential Medium with 10% fetal calf serum.

The medium was aspirated off the cultures and replaced with 1 ml. of growth medium [Eagle's Minimum Essential Medium with non-essential amino acids, prepared as described by Eagle, Science 130, 432 (1959)] and 10% fetal calf serum. The medium of paired cultures was supplemented with 500, 100, 20 and 4 α/ml. of the compound under test. Four cultures were used as untreated controls. The cultures were incubated at 34° C. in a roller drum (12 r.p.h.). After 3 days the cultures were examined microscopically for evidence of compound toxicity, i.e., alteration in cell morphology observed in unstained cultures at 100× magnification. The maximum compound concentration providing no indication of toxicity in either of the two cultures was the maximum well-tolerated concentration.

The tube cultures described above were then used for the activity determination. Five-tenths ml. of an appropriate dilution of virus in growth medium containing 10 $TCID_{50}$ (tissue culture infective dose, i.e., dose causing infection of 50% of the cultures) were added to 40 cultures. Five-tenths ml. of growth medium were added to four cultures to be used as cell controls. The cultures were then incubated at 34° C. Excess virus or growth medium was removed after 1 hour and 1 ml. of growth medium was added to each culture. Four non-infected cultures used as cell controls and eight infected cultures used as virus controls were maintained in upsupplemented medium. Eight infected cultures were used to deter-

mine the anti-viral activity of each compound concentration; these received 1, 1/5, 1/25, and 1/125 WTD (well tolerated dose) of test compound diluted with the growth medium. The cultures were rolled at 34° C. The cultures were examined microscopically after four days and scored on the basis of extent of cytopathic effect. The results are stated as a therapeutic ratio, which is the maximum concentration of compound tolerated by the cultures over the minimum concentration which inhibits cell destruction by the virus. 3-(3-acetoxypropylamino)-5-methyl-as-triazino[5,6-b]indole possesses a therapeutic ratio of 500/500–100 against rhinovirus strain 1059, 500/500–100 against strain HGP, and 500–100/<4–100 against strain 33342. 3 - (3 - methoxypropylamino)-5-methyl-as-triazino[5,6-b]indole possesses a therapeutic ratio of 500/20 against 1059, 500/100–500 against HGP, and 500/100 against 33342. 3 - [N - (3-acetoxypropyl) acetamido]-5-methyl-as-triazino[5,6-b]indole possesses a therapeutic ratio of 500–100/500–20 against 1059, 500/500 against HGP, and 500/500 against 33342. 3-(3-propionoxypropylamino) - 5 - methyl-as-triazino[5,6-b]indole possesses a therapeutic ratio of 500–100/500–100 against 1059 and 500/500 against HGP.

The compounds of the invention may be formulated for use in a manner well known to pharmaceutical chemists by combining them with standard pharmaceutical excipients to form tablets, capsules, ointments and intranasal preparations. The oral formulations may contain between 1 mg. and 1 g. and may be administered 1–4 times daily.

The preparation of these pharmaceutical compositions is illustrated below.

Capsules

300 kg. of 3-(3-acetoxypropylamino)-5-methyl-as-triazino[5,6-b]indole are finely divided in a comminuting mill to produce a 60 B.S. mesh powder. This powder is filled into No. 1 hard gelatin capsules so that each capsule contains 300 mg. of the active ingredient.

Tablets

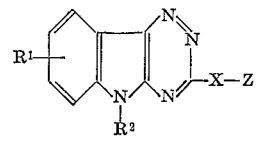
3.00 kg. of 3 - (3 - methoxypropylamino)-5-methyl-as-triazino[5,6-b]indole, 300 g. of maize starch, 400 g. of lactose and 80 g. of hydrolyzed gelatin are mixed together, then sufficient distilled water is added to produce a damp cohesive mass. The mass is passed through a 16 B.S. mesh screen to produce granules which are dried and then passed through a screen to produce 20 B.S. mesh granules. The dried granules are mixed with 300 g. of maize starch, 800 g. of microcrystalline cellulose, 60 g. of polyethylene glycol 4000 and 60 g. of magnesium stearate. The lubricated granules are compressed on a suitable tabletting machine to produce tablets each weighing 500 mg. and containing 300 mg. of 3-(3-methoxypropylamino)-5-methyl-as-triazino[5,6-b]indole.

Nasal suspension

100 g. of sodium carboxymethylcellulose of medium viscosity grade are dissolved in 5 liters of distilled water. When solution is complete, 20 g. of sodium citrate, 13 g. of potassium biphthalate, 0.1 g. of thiomersal and 2 ml. of eucalyptol are added. The mixture is stirred until solution takes place. 500 g. of 3-(3-acetoxypropylamino)-5-methyl-as-triazino[5,6-b]indole are slowly dispersed in the gel, and the volume is made up to 10 liters with distilled water.

We claim:

1. A compound of the formula:



wherein:

R^1 is hydrogen, halogen, alkyl of 1–4 carbon atoms, hydroxy, alkoxy of 1–4 carbon atoms, nitro, amino, or trifluoromethyl;

R^2 is hydrogen, lower alkyl of 1–4 carbon atoms, benzyl, or phenethyl;

X is NR^3, where R^3 is hydrogen, methyl, or lower alkanoyl of 1–4 carbon atoms;

Z is $AlkOR^6$, where Alk is a branched or straight chain alkylene of 2 to 10 carbon atoms; and

R^6 is lower alkanoyl of 1–8 carbon atoms or lower alkyl of 1–4 carbon atoms, or a pharmaceutically acceptable non-toxic acid addition salt thereof.

2. A compound as claimed in claim 1, in which R^1 is hydrogen, R^2 is methyl, and Alk is propylene or dimethylpropylene.

3. A compound as claimed in claim 1, in which R^1 is at the 8-position.

4. A compound as claimed in claim 1, which is 3-(3-acetoxypropylamino) - 5 - methyl - as - triazino[5,6-b]-indole.

5. A compound as claimed in claim 1, which is 3-(3-propionoxypropylamino)-5-methyl - as - triazino[5,6-b] indole.

6. A compound as claimed in claim 1, which is 3-(3-methoxypropylamino) - 5 - methyl - as - triazino[5,6-b]-indole.

7. A compound as claimed in claim 1, which is 3[3-(N - acetoxypropyl)acetamido] - 5 - methyl - as - triazino [5,6-b]-indole.

References Cited

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