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(54) IMPROVEMENTS IN OR RELATING TO SUBSTITUTED ACRYLONITRILES

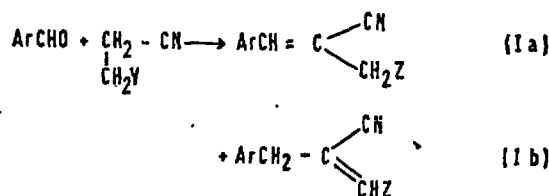
(71) We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1., a company incorporated in England do hereby declare the invention which was communicated from BURROUGHS WELLCOME & Co. (U.S.A.) INC., of 1, Scarsdale Road, Tuckahoe, New York 10707, a Company Incorporated in the State of New York, United States of America, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a class of stable α -benzylacrylonitriles, and to methods of making such compounds, and in one specific aspect to the value of such compounds for use in much improved processes of preparing 5-benzylpyrimidines.

2,4-Diamino-5-benzylpyrimidines possess both antimalarial and antibacterial activities. (*J. Am. Chem. Soc.*, 1951, 73, 3758). Maximal antibacterial activity is found among derivatives which bear electron donating substituents in the benzene nucleus and are unsubstituted in the 6th position of the pyrimidine moiety. 2,4-Diamino-5-(3',4',5'-trimethoxybenzyl) pyrimidine or trimethoprim (U.S. Patent 2,909,522) has a moderately broad antibacterial spectrum which includes many of the Gram-positive species but it is also active against species of the genus *Proteus*. In common with other 2,4-diaminopyrimidines it is a competitor of folic and folinic acids in microorganisms which require these nutrilites, and it can be shown to inhibit dihydrofolate reductase in *Streptococcus faecalis*. A strong potentiative effect is observed when the drug is administered in combination with sulphonamides as a consequence of the sequential blockade of the biochemical pathway which leads to the *de novo* synthesis of coenzymes F. This potentiation may be demonstrated both *in vitro* and in experimental infections in mice with *Staphylococcus* and *Proteus* species. 2,4-Diamino-5-benzylpyrimidines, which include trimethoprim and 2,4-diamino-5-(3',4'-dimethoxybenzyl)pyrimidine or diaveridine (U.S. Patent 2,658,897), may be administered orally at a dose of 1 mg/kg to 30 mg/kg per day. Preferably these compounds are administered in tablet form to a mammal being treated, and trimethoprim may advantageously be combined with sulphamethoxazole against certain respiratory infections. A further example of this class is 2,4-diamino-5-(2'-methyl-4',5'-dimethoxybenzyl)pyrimidine (ormetoprim), which has been reported to show antibacterial activity, and also has coccidiostatic properties when combined with sulphadimethoxine.

A new route was developed some years ago for the preparation of 2,4-diamino-5-benzylpyrimidines (see Stenbuck, Baltzly and Hood, *J. Org. Chem.*, 1963, 28, 1983 and British Patent Specification No. 957,797). This route comprises the steps of (i) condensing an aromatic aldehyde with a β -substituted propionitrile in the presence of

both an alcohol as solvent and a strong base to give a mixture of isomers of formulae (Ia) and (Ib) respectively:



wherein Ar is an optionally substituted phenyl group, Y is an alkoxy, alkylthio or dialkylamino group, and Z is the group Y or is an alkoxy group derived from the solvent alcohol; and

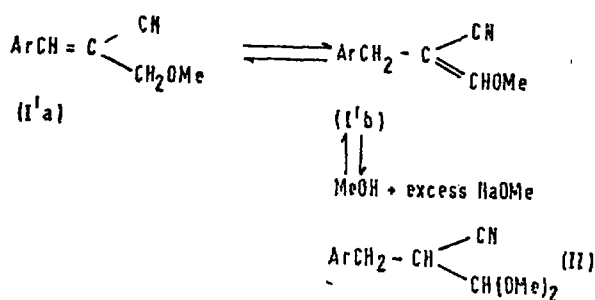
(ii) reacting either the pure 'benzal' isomer (Ia) or a mixture of 'benzal' and 'benzyl' isomers (Ia) and (Ib) respectively with guanidine to give a 5-benzylpyrimidine.

Although it was known that the intermediate product obtained in the first step was a mixture of isomers of formulae (Ia) and (Ib), only the (Ia) 'benzal' isomer could be isolated in a crystalline form after some purification steps. The two isomers were assumed to be in equilibrium with each other when prepared under alkaline conditions and further reacted with guanidine according to the aforesaid disclosures, but it was not clearly established which of the isomers was primarily interacting in the second step.

Unfortunately, there was also much evidence as to losses owing to formation of polymers and coloured impurities, especially in cases where the phenyl ring of the isomers was unsubstituted in the *para*-position.

The further conversion of composite mixtures of derivatives and isomers according to British Patent Specification No. 957,797 afforded the required 2,4-diamino-5-benzylpyrimidines only in yields between 25 and 45%, and in view of the importance of the final products and the difficulties with by-products and impurities, alternative methods were actively sought by various investigators.

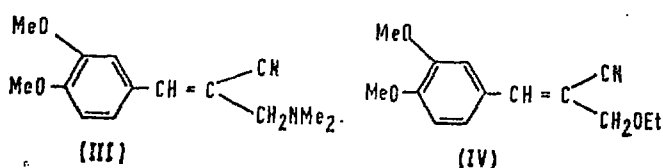
Subsequent developments showed that the polymer formation obtained when operating the process described in the specification of British Patent No. 957,797, could be prevented or reduced in cases of β -alkoxy-derivatives of compounds (Ia) and (Ib) by temporarily saturating the ethylenic double bond with excess alkoxide in alcohol. This provides the corresponding acetal of formula (II), for instance, according to the reaction outlined below:



When the acetal (II) is subsequently treated with guanidine in alcoholic solution, the alkaline condition is thought to catalyse the reconstitution of the double bond, initially in the form of (I'b), and the intermediate can thus react with guanidine to give the desired 5-benzylpyrimidine.

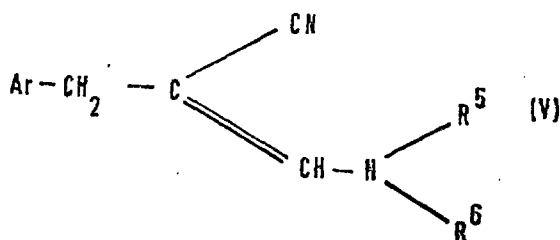
Acetals of formula (II) may also be prepared by condensing the corresponding aromatic aldehyde with a 3,3-dialkoxypropionitrile and reducing, preferably catalytically, the 3,3-dialkoxy-2-benzalpropionitrile intermediate so obtained.

The aforesaid British Patent Specification No. 957,797 also describes (Example 14) the reaction of veratraldehyde with β -dimethylaminopropionitrile in the presence of sodium in ethanol to give a mixture of β -dimethylaminoveratralnitrile (III) and β -ethoxyveratralnitrile (IV) in a 32% yield.



It is stated in the Example that this mixture was subsequently cyclised with guanidine to give 2,4-diamino-5-(3',4'-dimethoxybenzyl)-pyrimidine. It is to be noted that both the compounds (III) and (IV) above are 'benzal' derivatives.

It has now been found that *N*-substituted β -amino- α -benzylacrylonitriles of the configuration of formula (V)



in which Ar is as defined above and NR^5R^6 is as defined below, can be prepared remarkably readily under a conveniently wide variety of conditions and that the products so obtained are not only substantially free of contamination with the corresponding 'benzal' isomer but manifest an unexpected stability and capability of maintaining their configuration, yet also a high reactivity under a variety of reaction conditions. The 'benzal' configuration of these compounds shows little or no tendency to isomerise into the 'benzal' form prepared and exemplified in the British Patent Specification No. 957,797. Furthermore, the β -amino- α -benzylacrylonitriles are chemically reactive and can be converted with advantage into benzylpyrimidines or into other benzyl derivatives.

According to the present invention in one aspect therefore there is provided an *N*-substituted- β -amino- α -benzylacrylonitrile compound of the formula (V), in a form substantially free from contamination with the β -amino- α -benzylidenepropionitrile isomer. This term as used herein means that the contamination with the 'benzal' isomer is less than 10%, taken as a percentage of the amount of compound of formula (V). It is preferably below 5 or, advantageously below 2%. Usually the best methods for making the compound of formula (V) provide the product with less than 0.5% contamination and frequently no benzal isomer can be detected at all with analytical methods sensitive to even as low as 0.33% admixture. It has, on the other hand, been observed that contamination at or above the 10% level adversely effects the yield and quality of the final benzylpyrimidine product, and the appearance of purple or yellow discolorisation may aggravate the difficulties, especially isolation in a pure form, an essential requirement when the product is to be used clinically, there therefore being necessary many tedious, time-consuming and accordingly expensive purification steps.

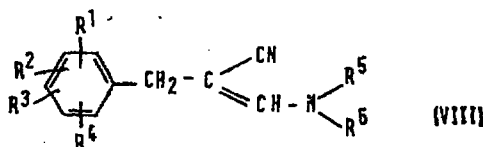
As previously defined Ar is an optionally substituted phenyl group in formula (V). The β -amino group NR^5R^6 is an aliphatic, heterocyclic or aromatic amino group, and can have only one hydrogen atom for R^5 and R^6 . In general it may be stated that, as a free amine, HNR^5R^6 is preferred to have a pK_a value not lower than 0, and most preferably not higher than about 6.

In particular, it is especially preferred that the NR^5R^6 group is an anilino group. The phenyl ring of this group may be optionally substituted with one or more substituents such as halogen atoms, and alkyl and alkoxy groups, but the unsubstituted anilino group is, however, particularly preferred. Other suitable examples of the amine HNR^5R^6 are *o*- and *p*-toluidine, *p*-anisidine, *p*-chloroaniline, 2,5-dichloroaniline, and 3,4-dichloroaniline.

The NR^5R^6 group may also be a secondary amino group other than the aforesaid anilino group, such as a monoalkylamino, benzylamino, or naphthylamino, preferably

β -naphthylamino group; or may be a tertiary amino group, such as a dialkylamino, pyrrolidino, piperidino, *N*-methylanilino, or a piperazino group such as the *N*-methylpiperazino group, or most preferably the morpholino group.

In particular the invention provides compounds of formula (VIII), in a form substantially free from contamination with the β -amino- α -benzylidene-propionitrile isomer, as hereinbefore defined:



wherein the group $\text{—NR}^5\text{R}^6$ is as hereinbefore defined with reference to a compound of formula (V), and R^1 , R^2 , R^3 and R^4 are the same or different and each is a hydrogen or a halogen atom, an alkyl, alkoxy, or benzyloxy group, or R^3 and R^4 taken together may be a methylenedioxy group when both R^1 and R^2 are hydrogen atoms.

In formulae (V) and (VIII), any alkyl or alkoxy substituents may have from 1 to 4 carbon atoms, e.g. they may be methyl, ethyl, propyl or butyl groups, including normal, iso or tertiary branched forms, and corresponding alkoxy groups. Any halogen substituent may be chlorine, bromine, fluorine or iodine. Preferably, the whole amino group NR^5R^6 comprises not more than 12 carbon atoms. More particularly the *para*-position of the phenyl group forming part of the benzyl group may be substituted with a benzyloxy, hydroxy, but preferably an alkoxy group, such as a methoxy group, especially with a similar or identical alkoxy substitution at one or advantageously both meta positions on the phenyl ring. As another possibility alkoxy, e.g. methoxy substitution, in such positions may be combined with a C_{1-4} alkyl, e.g. methyl, substitution at one of the *ortho*-positions of the phenyl group.

The compounds according to formula (V) or (VIII), respectively, may be prepared by a wide variety of methods. The actual choice between these methods in any particular instance depends primarily on the reactivity of the compound obtained, and the further processing to which it may be subjected to provide compounds such as pyrimidines of clinical utility, the further processing being itself governed to a great extent by the nature of the amino group NR^5R^6 , this acting as a leaving group in the further reactions.

Compounds according to formula (V) or (VIII) can be prepared by a method provided by the present invention, which comprises reacting the corresponding benzaldehyde with the corresponding β -aminopropionitrile in the presence of a base in a polar aprotic solvent compatible with and dissolving both reactants.

Polar aprotic solvents suitable for the purpose include hexamethylphosphoramide and *N,N*-dimethylacetamide, but best results have been obtained with dimethylsulphoxide as the solvent. Bases required for the reaction include those in which the anion is hydroxide, alkoxide, especially the alkoxides having from 1 to 4 carbon atoms, such as methoxide or *tert*-butoxide, or the methylsulphinyl carbanion, used in association with a suitable cation, such as an alkali metal (e.g. sodium or potassium) or a quaternary ammonium cation (e.g. *N*-benzyl-*N,N*-trimethylammonium).

Advantageously, the amount of base can be considerably reduced to "catalytic amounts", i.e. effective quantities of less than 0.3 molar equivalent calculated on the aldehyde used, particularly at temperatures above 60°C , preferably between 90°C and 130°C . For instance, very good yields have been obtained in this manner using dimethyl sulphoxide as the solvent.

Very satisfactory yields have also been obtained with the β -amino compounds of the invention such as β -anilino-substituted compounds with 0.5 to 2 molar equivalents of the base at room (about 20°C) or slightly elevated temperature up to about 60°C in the solvent. Dimethylsulphoxide may be replaced under these conditions as well by other polar aprotic solvents, especially hexamethylphosphoramide. It has been found most advantageous to use *t*-butoxide as the base in the form of the potassium salt in dimethylsulphoxide for the preparation of β -anilino-substituted compounds, whilst, for instance, the β -morpholino-analogue may be preferred to be formed in the presence of sodium methoxide in the same medium.

Compounds according to formula (V) or (VIII) can also be prepared by reacting the corresponding (β -hydroxy- β -phenylethyl) methyl sulphone or sulphoxide with the corresponding β -amino-propionitrile. Very preferably the reactions carried out in the presence of a base in a polar non-aqueous solvent compatible with and dissolving

both reactants of elevated temperatures above 30°C. The solvent may be an alkanol, such as methanol, ethanol or isopropanol, or most conveniently a polar aprotic solvent such as exemplified above. The base is preferably sufficiently strong on its own for a significant amount of the sulphone or sulfoxide reactant to be converted into the anionic form. Again hydroxides or alkoxides, preferably methoxide or t-butoxide, in the form of an alkali metal salt, have been found very convenient for the purpose. The method is especially suitable for making compounds in which NR^5R^6 is anilino and is particularly advantageous with alkoxy substitutions on the *para* and/or *meta* positions of the phenyl groups Ar, since the appropriate starting materials are most readily prepared in such instances.

The required (β -hydroxy- β -phenethyl) methyl sulphone or sulfoxide for the above method, may conveniently be provided by a process which comprises the steps of reacting an appropriately substituted benzoic acid ester with dimethyl sulphone or dimethyl sulfoxide preferably in the presence of a base, and selectively reducing the so obtained methyl phenacyl sulphone or sulfoxide derivative, for instance, with a suitable borohydride or with aluminium isopropoxide.

A further method of preparing a compound according to formula (V) or (VIII) is provided by the present invention, this method comprising reacting the corresponding β -hydroxy- α -benzylacrylonitrile with the appropriate amine. Preferably if a solvent is used it is a non-aqueous solvent such as benzene or an alkanol, e.g. ethanol, and it has been found convenient to carry out the reaction at elevated temperatures, particularly at reflux.

This method helps to establish and demonstrate that the compounds according to formula (V) or (VIII) retain their stability and 'benzyl' configuration, yet may be suitable for inter-conversion into each other in respect of the amino group. In particular the conversion may efficiently be carried out by a process comprising the hydrolysis of the first amine, most preferably an aliphatic or heterocyclic amine to provide the appropriate β -hydroxy- α -benzyl-derivative, and the subsequent reaction of the product with the second amine, as hereinbefore defined. The required β -hydroxy- α -benzylacrylonitrile may thus be provided by hydrolysing the corresponding β -amino- α -benzylacrylonitrile, conveniently with an acid in an aqueous medium. Preferably a dilute solution of a mineral acid, such as hydrochloric is used for the purpose. For instance, a β -morpholino- α -benzylacrylonitrile has thus been converted into the corresponding β -hydroxy-derivative almost instantaneously and in nearly quantitative yield. The product may then be extracted with an organic solvent from an aqueous medium, and isolated, or immediately reacted with a different amine to obtain a compound according to formula (V) or (VIII). In both instances it has been found that the β -hydroxy- α -benzylacrylonitriles are generally as a class particularly stable materials, there being little or no tendency to isomerisation to the 'benzal' form during these manipulations.

Such a conversion from one amino derivative to another may be achieved in a very high yield, in many instances above 90% in both steps, and the product so obtained can be reacted to form other materials such as benzylpyrimidines in a quality and yield often even better than that provided by using the original β -amino-derivative.

In addition, this method may be very advantageous for preparing certain β -amino- α -benzylacrylonitriles, especially in cases where the NR^5R^6 group is a basic but only weakly basic anilino group, e.g. *p*-chloro-anilino. In such instances, there are sometimes difficulties in preparing the corresponding β -anilino-propionitrile for reaction with the benzaldehyde.

Yet further methods provided by the present invention may be used to obtain selected or preferred ranges of compounds within the scope of formula (V) or (VIII). Accordingly, a method is provided for preparing such compounds, wherein the β -amino group NR^5R^6 is an anilino group optionally substituted in the phenyl ring, as hereinbefore defined, which comprises reacting the corresponding benzaldehyde with the corresponding β -anilino-propionitrile. Preferably the reaction is carried out in a polar non-protic solvent compatible with and dissolving the reactants in the presence of a base. Conveniently a lower alkanol having from 1 to 4 carbon atoms may be used for the purpose, and the reaction is desirably carried out at elevated temperatures, say between 40° and 80°C. The preferred alkanol is methanol, particularly when the reactant benzaldehyde is substituted with one or more methoxy groups, since it is possible for exchange to take place between the solvent and the substituents. Bases already listed in relation to the other preparatory methods are again applicable, and may, for instance, be used in a quantity more than 1 molar equivalent calculated on

the aldehyde, especially when the reaction is carried out at the lower end of the indicated temperature range.

The above defined group of β -anilino- α -benzylacrylonitriles can also be prepared by a method which comprises reacting the corresponding aniline, generally in the form of an acid addition salt, for example an acetate or hydrochloride salt with a compound of formula (V) or (VIII) carrying an amino substituent which has, as the free amine HNR^5R^6 , a pK_a value higher by at least 3, for example at least 4, units than that of the aniline used for the reaction. For instance, a morpholino substituent may, in this manner, be directly replaced by an anilino substituent, morpholine having a pK_a value of about 8.6 and the aniline generally about 4 to 5. Preferably the reaction is carried in a polar non-aqueous solvent system, for instance, ethanol or glacial acetic acid, at reflux temperatures.

Compounds according to formula (V) or (VIII), wherein the β -amino group NR^5R^6 is a secondary amino group other than anilino, or is a tertiary amino group, can also be prepared according to the present invention by reacting the corresponding β -alkoxy- α -benzylidenepropionitrile with an excess of the appropriate amine in the presence of a base in an alkanol. Suitable bases are again those already listed for other methods. Preferably the base is the alkoxide corresponding to the solvent. For instance, a β -methoxy- α -benzylidenepropionitrile may be so converted with morpholine, in methanol containing a methoxide, e.g. sodium methoxide, to the corresponding β -morpholino- α -benzylacrylonitrile.

The above group of compounds according to formula (V) or (VIII), wherein the β -amino-group NR^5R^6 is other than an anilino group, can moreover be prepared according to the present invention by isomerising the corresponding β -amino- α -benzylidene-propionitrile isomer with a base in a polar aprotic solvent. Under these conditions the 'benzal' isomer is isomerised into the 'benzyl' form, there appearing to be little or no 'benzal' isomer after the process. Suitable aprotic polar solvents and bases are as hereinbefore described with reference to other reactions, and the most preferred solvent is again dimethylsulphoxide and the most convenient bases those in which the anions are the methoxide and *t*-butoxide anions. Normally there is at least 0.01, and preferably about 0.1, molar concentration of base present in the solvent, and often not more than about 1 molar concentration, though as high as 2 or even 4 molar concentrations may be used. The quantity of solvent is not critical though there is preferably sufficient throughout the isomerisation to dissolve the nitrile. The isomerisation can be effected at room temperature but is most conveniently carried out in the presence of heat, particularly good yields being obtained when it is carried out at a temperature above 20°C. and up to 75°C. or even higher. The method has been very successfully applied to β -morpholino- α -benzylidene-propionitriles, in particular to those having a 3,4-dimethoxy or 3,4,5-trimethoxy-benzylidene group.

The starting 'benzal' isomer, i.e. the appropriate β -amino- α -benzylidene-propionitrile, for the purposes of the above reaction, can advantageously be prepared by reacting the corresponding benzaldehyde with the corresponding β -amino-propionitrile in an alkanol in the presence of a "catalytic amount" of a base, in the sense hereinbefore used in the present specification, which means an effective quantity of less than 0.3 molar equivalent calculated on the aldehyde reagent.

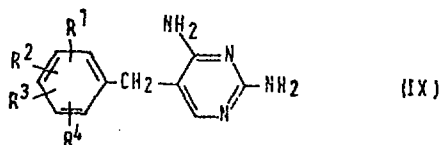
Alkanols in this reaction are generally lower alkanols, having from 1 to 4 carbon atoms, methanol being particularly preferred. Suitable bases are again those already suggested in connection with base catalysed condensation reactions, but methoxides and *tert*-butoxides, particularly the former, are preferred for the present purpose. Best results may be obtained at elevated temperatures, and it is particularly preferred to carry out the reaction at reflux temperatures.

As already indicated, the optimum route for preparing any particular compound according to formula (V) or (VIII) may comprise a combination of a number of the above processing possibilities, depending primarily on the type of amino NR^5R^6 group required. For instance, β -anilino- α -3',4',5'-trimethoxy-benzylacrylonitrile has certain especial advantages as an intermediate for the preparation of trimethoprim. Thus, the reaction of guanidine with β -anilino- α -benzylacrylonitriles generally proceeds appreciably faster than that with other β -amino derivatives as defined by formula (V) or (VIII).

The β -anilino-intermediate can moreover be produced readily without any 'benzal' isomer detectable by standard analytical methods, and can be further processed to 2,4-diamino-5-benzylpyrimidines in a very high yield there being little or no polymer formation at all. It is most noteworthy that the reaction with guanidine is readily effected under mild conditions, and both the preparation of the intermediate and the further processing may be completed within hours rather than weeks.

Whilst β -anilino- α -benzylacrylonitriles may be readily prepared by a wide variety of advantageous methods, the choice in any particular instance depends partly upon the availability of the starting material, and, for instance, β -anilino-propionitrile, when prepared from aniline and acrylonitrile, usually requires isolation and purification before use. In contrast, the corresponding β -morpholino-propionitrile can be readily formed and need not be isolated. Furthermore, in cases of trimethoxy-substituted benzyl derivatives, and base catalysed reactions, the cheaper and more widely available sodium methoxide is preferred for morpholino-derivatives, whilst the more expensive potassium *t*-butoxide generally gives best results for anilino-compounds. It may therefore on occasion be advantageous to prepare the morpholino-intermediate first and convert this into the corresponding anilino derivative to obtain optimum results.

According to the present invention in a further aspect there is provided a method of preparing 2,4-diamino-5-benzylpyrimidines, wherein the benzyl group comprises an optionally substituted phenyl group, by reacting the corresponding β -amino- α -benzylacrylonitrile of formula (V), substantially free from contamination with the β -amino- α -benzylidene-propionitrile isomer, as hereinbefore defined, with guanidine. In particular a method is provided of preparing a compound of formula (IX)



which comprises reacting a compound of formula (VIII) substantially free from contamination with the β -amino- α -benzylidenepropionitrile isomer, as hereinbefore defined, with guanidine; in formula (IX) R^1 , R^2 , R^3 and R^4 are as defined for formula (VIII). It has been found that the pyrimidine products are obtained in a satisfactorily high yield as well as without contamination with polymers and coloured impurities. These aspects are of critical importance as indicated hereinbefore, since contemporary requirements for the purity of pharmaceutical products are very stringent and the products must be manufactured in a very pure form and, of course, at a reasonable cost. Both these necessities are now more readily attainable, as a result of the present invention, for the benzylpyrimidines.

To obtain 5-benzylpyrimidines having particularly high activity, or potentiating properties, the *para* position of the phenyl group is preferably substituted with an alkoxy, i.e. methoxy group, especially in combination with a similar substitution at one or both adjacent *meta* positions. Such substitutions may also be present when at least one of the *ortho*-positions is occupied by an alkyl group having from 1 to 4 carbon atoms, such as methyl. The pyrimidines are then trimethoprim, diaveridine, ormetoprim and analogues thereof.

For the purposes of obtaining 5-benzylpyrimidines or in particular those of formula (IX) preferably having the above mentioned specific substituents, the appropriate β -anilino-derivatives have been found particularly useful. Advantageously such an amine is reacted with guanidine, conveniently in a solvent which comprises an alkanol having from 1 to 4 carbon atoms, for example, methanol, ethanol, or isopropanol, at elevated temperatures. It is particularly preferred that the reaction is carried out at the reflux temperature of the reaction mixture but useful rates are found at lower temperatures down to room temperatures. It has been found specifically that the reaction at reflux temperatures takes place very readily, taking hours rather than weeks for completion.

Although the reactivity with guanidine of β -amino- α -benzylacrylonitriles of formula (V) or (VIII), other than those having a β -anilino group, such as the morpholino derivatives is lower, particularly in alkanols, it has been found that this can be increased and the yield substantially improved if the guanidine is employed in the form of the carbonate in a polar aprotic solvent, as hereinbefore described with reference to other methods, e.g. especially dimethylsulphoxide or hexamethylphosphoramide. The reaction is slow below 140°C, but goes rapidly at about 160°C or above. Best results have been obtained in these particular cases with dimethylsulphoxide at or near refluxing temperatures; and, if the previous reaction step has also been carried out in the same medium, the β -amino- α -benzylacrylonitrile intermediate need not be isolated, although isolation is usually preferred since purer benzylpyrimidine is obtained in this manner.

All end products provided in the above manner have either antibacterial activity or potentiating properties, although the degree of such activity and potentiating effect may vary according to substitution and the purpose for which these compounds are employed. Moreover, the products may themselves be used as starting materials to produce other derivatives and analogues by further reactions with functional groups thereon. Thus benzyloxy-benzyl-derivatives may, for instance, be converted into the corresponding hydroxy-benzyl-derivatives by hydrogenation, or any hydroxy-benzyl-derivatives alkylated to provide the required alkoxy-benzyl-substituted compounds.

According to the present invention, therefore, there are provided:

(i) *N*-substituted- β -amino- α -benzylacrylonitrile compounds according to formula (V) or, in particular, formula (VIII), substantially free from contamination with β -amino- α -benzylidenepropionitrile, as hereinbefore described:

(ii) the various methods of preparing the compounds defined in (i) above, as hereinbefore described;

(iii) *N*-substituted β -amino- α -benzylacrylonitriles whenever prepared by a method defined under paragraph (ii), as hereinbefore described;

(iv) the methods of preparing (β -hydroxy- α -benzylacrylonitriles) from *N*-substituted β -amino- α -benzylacrylonitriles;

(v) methods of preparing 5-benzylpyrimidines by using compounds or products of methods, according to any one of paragraphs (i) to (iii), as hereinbefore described;

(vi) 5-benzylpyrimides whenever prepared by a method according to paragraph (v).

The present invention, in each of the above aspects, is particularly preferred when the phenyl group is a 3,4-dimethoxy, 3,4,5-trimethoxy or 2-methyl-4,5-dimethoxy group, since there are then produced the especially valuable compounds diaveridine, trimethoprim or ormetoprim, or the respective intermediates therefor.

The following Examples 1 to 44, 52 to 84 illustrate the invention Examples 45 to 51 illustrate the preparation of starting materials for use in the invention.

EXAMPLE 1

3,4,5-Trimethoxybenzaldehyde (98 g.), β -anilino-propionitrile (85 g.), and dimethylsulphoxide (175 ml.) were heated together to 125°C. A solution of sodium methoxide (5 g.) in methanol (50 ml.) was gradually added and in so doing the reaction temperature rose to 130°C, and this temperature was maintained for a further 17 minutes. The reaction mixture was chilled; water was added to a persistent haze; seeds of β -anilino- α -3,4,5-trimethoxybenzylacrylonitrile were added; and the mixture was stirred at 25°C until precipitation was copious. Additional water (400 ml.) was added, and the product was collected by filtration and reslurried in ice water (600 ml.). The collection and reslurry procedures were repeated using cold (~5°C) denatured ethanol (320 ml.), and the crystalline β -anilino- α -3,4,5-trimethoxybenzylacrylonitrile was finally collected; washed with cold denatured ethanol (40 ml.), and hexane (100 ml.). Wt.=115 g. (98% pure by U.V. assay), m.p. 132–133°C (recrystallised from methanol).

EXAMPLE 2

3,4,5-Trimethoxybenzaldehyde (49 g.), β -anilinopropionitrile (40 g.) and dimethylsulphoxide (85 ml.) were heated to 130°C and a solution of potassium hydroxide (2.5 g.) in methanol (12.5 ml.) was added over a 35 minute period. The temperature of the reaction was maintained at 132–133°C for an additional 30 minutes. The reaction mixture was then treated as in Example 1 and gave β -anilino- α -3,4,5-trimethoxybenzylacrylonitrile as a crystalline solid. Wt.=57 g.

EXAMPLE 3

3,4,5-Trimethoxybenzaldehyde (117.5 g.; 0.6 mole), β -anilino-propionitrile (101 g.; 0.69 mole) and dry distilled dimethylsulphoxide (348 ml.) were heated together to 40°C until complete solution occurred. The mixture was chilled to 12°C and a 13.6% solution of potassium *t*-butoxide in *t*-butanol (491 ml.; 0.6 mole) added over the course of about 10 minutes with additional cooling such that the final temperature was about 30°C. The reaction temperature was raised to 40°C and maintained for one hour. *t*-Butanol was stripped from the reaction using vacuum to a final pot temperature of 55°C. The residue was chilled to 30°C and water (100 ml.) and denatured ethanol (50 ml.) added. The mixture was seeded and, after obvious crystallisation, more ice and water (500 ml.) and denatured ethanol (75 ml.) were added. The final temperature of the mixture was 5–10°C. The crystalline α -3,4,5-trimethoxy-

8	9	1,261,455	9
activity iating ounds als to roups to the enzyl- inds.		oxybenzyl- β -anilinoacrylonitrile was collected and washed with cold water/denatured ethanol (85:15, 600 ml.) Wt.=181.7 g. (94% pure by U.V. assay).	
		EXAMPLE 4	
5	5	3,4-Dimethoxybenzaldehyde (88 g.), β -anilinopropionitrile (82.5 g.), dimethylsulphoxide (160 ml.) and sodium methoxide (6 g.) were heated together at 95°C for 2½ hours. The reaction mixture was then chilled to 25°C and diluted with isopropanol (40 ml.) and water (60 ml.). When crystallisation was obvious, further water (200 ml.) was added. The mixture was cooled to 5°C and the crystalline β -anilino- α -3,4-dimethoxybenzylacrylonitrile was collected and washed with cold water/isopropanol (1:1). Wt. 99 g. (61%), m.p. 153—154°C (recrystallised from denatured ethanol).	5
formula th β -	10	10	10
c, as		EXAMPLE 5	
ethod	15	Piperonaldehyde (45 g.), β -anilinopropionitrile (52 g.) and dimethylsulphoxide (96 ml.) were heated together to 120°C and a solution of sodium methoxide (2.5 g.) in methanol (12 ml.) was added over a 5 minute period. The temperature was maintained at 115—120°C for a 1 hour period and the reaction mixture was then poured into ice-water. The resulting gum was collected by decantation and was likewise washed with water (2×100 ml.). Methanol (100 ml.) was then added and the mixture was heated until solution was complete. Cooling to 5°C gave β -anilino- α -piperonylacrylonitrile as a crystalline solid which was collected and washed with cold methanol, ether and pentane. Wt.=45 g., m.p. 150.5—151°C (recrystallised from methanol).	15
-sub-	15		15
ts of d; graph	20	20	20
erred meth- veri-	25	EXAMPLE 6	
s 45		The procedure of Example 3 was repeated using 3,4-dimethoxy-5-bromobenzaldehyde (78 g.) and gave β -anilino- α -3,4-dimethoxy-5-bromobenzylacrylonitrile. Wt.=62 g., m.p. 151—154°C.	
	25	EXAMPLE 7	25
di- lium reac- ther aze; ture was (600 de- zyl- and (re-	30	Sodium methoxide (5.4 g.) in t-butanol (50 ml.) was slowly treated with a solution of 3,4,5-trimethoxybenzaldehyde (20 g.) and β -(<i>p</i> -methylanilino)propionitrile (17.5 g.) in dimethylsulfoxide (50 ml.). The mixture was stirred at 45°C for one hour and the ethanol was then removed in vacuo (maximum bath temperature 50°C). The mixture was poured into ice/water and the crude product collected and recrystallised from methanol (100 ml.) to give β -(<i>p</i> -methylanilino)- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=30 g., m.p. 150—151°C (recrystallised from methanol).	30
	30		30
	35	EXAMPLE 8	
	35	The procedure of Example 7 was repeated using β -(<i>p</i> -chloroanilino)propionitrile (20 g.) in place of β -(<i>p</i> -methylanilino) propionitrile. Wt. of recrystallised β -(<i>p</i> -chloroanilino)- α -3,4,5-trimethoxybenzylacrylonitrile=24 g., m.p. 172—173°C (recrystallised from methanol).	35
	40	EXAMPLE 9	
di- side ture The -tri-	45	The procedure of Example 7 was repeated using β -(<i>p</i> -methoxyanilino) propionitrile (19.5 g.) in place of β -(<i>p</i> -methylanilino) propionitrile. Wt. of recrystallised β -(<i>p</i> -methoxyanilino)- α -3,4,5-trimethoxybenzylacrylonitrile=11 g., m.p. 125—126°C (recrystallised from methanol).	40
	40		40
	45	EXAMPLE 10	
	45	2-Methyl-4,5-dimethoxybenzaldehyde (18 g.), dimethylsulphoxamide (35 ml.), sodium methoxide (1.0 g.), and β -anilino-propionitrile were heated together at 95°C for 1½ hours. The mixture was then poured into ice-water (150 g.), and the resulting solid collected by decantation. The crude product was recrystallised from methanol (100 ml.), and the resulting β -anilino- α -(2-methyl-4,5-dimethoxybenzyl) acrylonitrile was collected, and washed with methanol and hexane. Wt.=19 g., m.p. 117—119°C (recrystallised from ethanol/methanol).	45
101 her A a ver ure for m- de- tal- ed. th-	50	50	50
	55	EXAMPLE 11	
	55	<i>p</i> -Benzyloxybenzaldehyde (25 g.), β -anilinopropionitrile (22 g.), and dimethylsulphoxide (25 ml.) were heated together to 95°C, and a slurry of sodium methoxide (1 g.) in dimethylsulphoxide (20 ml.) was carefully added so that the temperature rose to 105°C. The mixture was heated to 125—130°C and held at that temperature for 1½ hours. The reaction mixture was poured into ice-water (500 ml.), and the resulting solid was collected and washed by decantation. The crude product was	55
	60		

slurried in cold ethanol to give β -anilino- α -(*p*-benzyloxybenzyl) acrylonitrile. Wt.=27 g.

EXAMPLE 12

5 β -Morpholinopropionitrile (47 g.), sodium methoxide (2 g.), and dimethylsulphoxide (40 ml.) were heated together to 65°C, and a solution of 3,4,5-trimethoxybenzaldehyde (50 g.) in dimethylsulphoxide (40 ml.) was added slowly such that the temperature rose to 70–75°C. After 3 minutes at this temperature, the mixture was cooled to 30°C, and isopropanol (30 ml.) and water sufficient to create a persistent haze were added. The mixture was seeded and, after crystallisation was obvious, 10 water (80 ml.) was added. Crystalline β -morpholino- α -3,4,5-trimethoxybenzylacrylonitrile was collected and washed with isopropyl alcohol (50 ml.). Wt.=73.5 g., m.p. 115–117°C (recrystallised from methanol). 10

EXAMPLE 13

15 3,4,5-Trimethoxybenzaldehyde (20 g.), β -N-methylanilinopropionitrile (18 g.), dimethylsulphoxide (40 ml.), and sodium methoxide (1 g.) were heated together at 110–115°C for 1.5 hour. The mixture was poured into ice-water (800 ml.) and the crude product which precipitated gave crystalline β -N-methyl-anilino- α -3,4,5-trimethoxybenzylacrylonitrile after a slurry in methanol (50 ml.). Wt.=17 g., m.p. 121–122°C (recrystallised from methanol). 15

EXAMPLE 14

20 3,4,5-Trimethoxybenzaldehyde (50 g.), β -piperadinopropionitrile (40 g.), dimethylsulphoxide (60 ml.), and sodium methoxide (2 g.) were reacted together at 75°C for 20 minutes and on work-up gave β -piperidino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=40 g., m.p. 92–93°C (recrystallised from methanol). 20

EXAMPLE 15

25 3,4,5-Trimethoxybenzaldehyde (25 g.), β -pyrrolidinopropionitrile (20 g.), dimethylsulphoxide (25 ml.) and sodium methoxide (1 g.) were reacted together at 75°C for 10 minutes and on work-up gave β -pyrrolidino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=28 g., m.p. 123–124°C (recrystallised from methanol). 25

EXAMPLE 16

30 3,4,5-Trimethoxybenzaldehyde (25 g.), β -dimethylaminopropionitrile (16 g.), dimethylsulphoxide (45 ml.), and sodium methoxide (1 g.) were reacted together at 70°C for 10 minutes, and on work-up gave β -dimethylamino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=25 g., m.p. 122–123°C (recrystallised from methanol). 30

EXAMPLE 17

35 3,4,5-Trimethoxybenzaldehyde (50 g.), β -benzylaminopropionitrile (45 g.), dimethylsulphoxide (80 ml.), and sodium methoxide (2 g.) were heated together at 100°C for 2 hours, and on work-up gave β -benzylamino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=32 g., m.p. 130.5–131°C. (recrystallised from methanol). 35

EXAMPLE 18

40 3,4,5-Trimethoxybenzaldehyde (25 g.), β -morpholinopropionitrile (20 g.), sodium methoxide (2 g.), and N,N-dimethylacetamide (25 ml.) were reacted together at 90–95°C for 1½ hours, and on work-up gave β -morpholino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=15 g. 40

EXAMPLE 19

45 β -N-methylpiperazinopropionitrile (23 g.) was reacted according to Example 16 to give β -N-methylpiperazino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=25 g., m.p. 141–143°C (sample recrystallised from methanol). 45

EXAMPLE 20

50 β -Morpholinopropionitrile (40 g.), dimethylsulphoxide (40 ml.), and sodium methoxide (2 g.) were heated together at 70°C and a solution of 3,4-dimethoxybenzaldehyde (44 g.) in dimethylsulphoxide (40 ml.) was added. The reaction was held at 75–80°C for 15 minutes, and then worked-up as in Example 12 to give crystalline β -morpholino- α -3,4-dimethoxybenzylacrylonitrile. Wt.=41 g., m.p. 130–131°C (recrystallised from methanol). 55

EXAMPLE 21

The procedure of Example 20 was repeated using β -dimethylaminopropionitrile (28 g.) in place of β -morpholinopropionitrile, and work-up gave β -dimethylamino- α -3,4-dimethoxybenzylacrylonitrile. Wt.=31 g., m.p. 85—86°C (recrystallised from methanol).

EXAMPLE 22

β -Morpholinopropionitrile (20 g.), dimethylsulphoxide (30 ml.), and sodium methoxide (1 g.) were heated together at 80°C and a solution of piperonaldehyde (19 g.) in dimethylsulphoxide was added. The mixture was reacted at 80°C for 15 minutes, and on work-up gave β -morpholino- α -piperonylacrylonitrile. Wt.=21 g., m.p. 85—85.5°C (recrystallised from methanol).

EXAMPLE 23

The procedure of Example 22 was repeated using 3,4-dimethoxy-5-bromobenzaldehyde (31 g.) in place of piperonaldehyde and on work-up gave β -morpholino- α -3,4-dimethoxy-5-bromobenzylacrylonitrile. Wt.=28 g., m.p. 94.5—95°C (recrystallised from denatured ethanol).

EXAMPLE 24

a) β -Hydroxy- α -3,4,5-trimethoxybenzylacrylonitrile (132 g.), obtained as hereinafter described in Example 66 was refluxed for 10 minutes in benzene containing aniline (50 g.). The solvent was removed by evaporation in vacuo to provide crystalline β -anilino- α -3,4,5-trimethoxybenzylacrylonitrile (165 g.; virtually theoretical yield).

b). β -Hydroxy- α -3,4,5-trimethoxybenzylacrylonitrile (25 g.), denatured ethanol (70 ml.) and 2,4-dimethylaniline (14 ml.) were refluxed together for one hour. The solvent was removed by evaporation in vacuo and the residue was poured into ice-water. The resulting thick gum was collected and recrystallised from methanol (100 ml.) to give crystalline β -2,4-dimethylanilino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=11 g., m.p. 123—125°C.

c). The procedure of Example 24b. was repeated using 3,4,5-trimethoxyaniline and gave β -3,4,5-trimethoxyanilino- α -3,4,5-trimethoxybenzylacrylonitrile in 65% yield. m.p. 156—161°C (recrystallised from denatured ethanol).

d). The procedure of Example 24b. was repeated using 2,5-dichloroaniline and gave β -2,5-dichloroanilino- α -3,4,5-trimethoxybenzylacrylonitrile (20 g.). A sample recrystallised from denatured ethanol melted at 130°C; resolidified; and then re-melted at 150°C.

e). The procedure of Example 24b. was repeated using α -naphthylamine (14.3 g.) and gave crystalline β -1-naphthylamino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=26 g., m.p. 107—109°C.

EXAMPLE 25

A solution of morpholine (10 ml.) and β -hydroxy- α -3,4,5-trimethoxybenzylacrylonitrile (24.9 g.) in ethanol (100 ml.) was refluxed for 30 minutes. When cooled the reaction gave β -morpholino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=27 g., m.p. 116—117°C.

EXAMPLE 26

Gallic acid trimethyl ether (565 g.) and methanol (2300 ml.) were mixed and the mixture then heated to 55°C for 5 hours. While anhydrous hydrogen chloride (46 g.) was passed into the mixture. The reaction mixture was poured into an ice and water mixture (8 litres) containing 10N sodium hydroxide solution (290 ml.) under stirring. The slurry of solids was filtered and the residue washed with ice water and dried in vacuo at 50°C to give methyl 3,4,5-trimethoxy benzoate, wt.=523 g., m.p. of 87—83°C.

Sodamide (27 g. 0.69 m), dimethylsulphoxide (225 ml.) and dimethylsulphone (56.5 g. 0.6 m) were heated together to 55°C for one hour and cooled to 50°C. Methyl 3,4,5-trimethoxybenzoate (65.4 g. 0.29 mole) was added, and the mixture heated to 60°C for one hour to complete the reaction.

- The mixture was poured into ice (1100 g.), acidified with dilute (1:1 hydrochloric acid (150 ml.) and cooled in an ice bath. The crystalline product was filtered off, washed with ice water (2×150 ml.) and ice-cold ethanol (2×100 ml.). Air drying overnight gave methyl 3,4,5-trimethoxyphenacyl sulphone, wt.=74 g., m.p. 147—148°C.
- 5 Methyl 3,4,5-trimethoxyphenacyl sulphone (38.1 g.), desalted water (100 ml.) and ethanol (30 ml.) were mixed and cooled to 15°C. A pre-cooled solution of sodium borohydride (2 g.) in desalted water (40 ml.) was gradually added. The cooling bath was then removed and the reaction mixture stirred for one hour. The slurry was cooled to 2°C, the solids filtered, washed with iced water, and dried in vacuo at 50°C to give 34.2 g. of the corresponding methyl[β-hydroxy-β-(3,4,5-trimethoxyphenyl)ethyl] sulphone, m.p. 153—154°C.
- 10 a). The above sulphone (29 g.), β-anilinopropionitrile (16.5 g.), and dimethylsulphoxide (40 ml.) were heated together to 40°C, and a solution of potassium t-butoxide in t-butanol (13.6%; 83 ml.) was carefully added. The temperature was maintained at 45°C for one hour. The alcohol was then removed from the reaction mixture by vacuum evaporation and the residue was poured into ice-water (200 ml). The crude crystalline product was collected and recrystallised from ethanol to give β-anilino-α-3,4,5-trimethoxybenzylacrylonitrile. Wt.=26 g. (after washing with ethanol and hexane).
- 20 Under the conditions described above under a). the following sulphones were condensed with β-anilinopropionitrile to yield the corresponding β-anilino-α-halogenobenzylacrylonitriles:
- 25 b). [β-hydroxy-β-(3,4-dichloro-phenylethyl)] methyl sulphone produced β-anilino-α-3,4-dichlorobenzylacrylonitrile;
- c). [β-hydroxy-β-(2-iodophenyl)ethyl] methyl sulphone produced β-anilino-α-2-iodobenzylacrylonitrile;
- d). [β-hydroxy-β-(3-iodophenyl)ethyl] methyl sulphone produced β-anilino-α-3-iodobenzylacrylonitrile;
- 30 e). [β-hydroxy-β-(4-iodophenyl)ethyl] methyl sulphone produced β-anilino-α-4-iodobenzylacrylonitrile;
- f). [β-hydroxy-β-(2-bromophenyl)ethyl] methyl sulphone produced β-anilino-α-2-bromobenzylacrylonitrile.
- 35 **EXAMPLE 27**
The procedure of Example 26 was repeated using hexamethylphosphoramide (40 ml.) in place of dimethylsulphoxide, and on work-up β-anilino-α-3,4,5-trimethoxybenzylacrylonitrile was obtained. Wt.=26 g. m.p. 126—128°C.
- 40 **EXAMPLE 28**
[β-Hydroxy-β-(3,4,5-trimethoxyphenyl)ethyl] methyl sulphone (5 g.), β-anilino-propionitrile (3 g.) dimethylsulphoxide (20 ml.) and a solution of potassium hydroxide in methanol (20%; 2 ml.) were reacted together at 90—95°C for 20 minutes. Work-up gave β-anilino-α-3,4,5-trimethoxybenzylacrylonitrile (3 g.) m.p. 126—129°C (recrystallised from ethanol).
- 45 **EXAMPLE 29**
The procedure of Example 28 was repeated using hexamethylphosphoramide (20 ml.) in place of dimethylsulphoxide and on work-up gave β-anilino-α-3,4,5-trimethoxybenzylacrylonitrile (2 g.) m.p. 125—127°C (recrystallised from ethanol).
- 50 **EXAMPLE 30**
The procedure of Example 28 was repeated using sodium methoxide (0.5 g.) in place of potassium hydroxide in methanol, and on work-up gave β-anilino-α-3,4,5-trimethoxybenzylacrylonitrile. Wt.=3 g., m.p. 128—130°C.
- EXAMPLE 31**
β-Hydroxy-β-(3,4,5-trimethoxyphenyl)ethyl] methyl sulphone (10 g.), β-anilino-propionitrile (5.1 g.), hexamethylphosphoramide (20 ml.), and sodium methoxide (1

EXAMPLE 41

- 5 3,4-Dimethoxybenzaldehyde (41.5 g.), β -anilinopropionitrile (38.5 g.), sodium methoxide (40 g.) and methanol (200 ml.) were reacted under reflux for 3 hours. The solvent was then removed by evaporation in vacuo and the resulting paste was re-crystallised from methanol to give β -anilino- α -3,4-dimethoxybenzylacrylonitrile. Wt.=55 g., m.p. 153—154°C (recrystallised from ethanol). 5

EXAMPLE 42

- 10 β -Morpholino- α -3,4,5-trimethoxybenzylacrylonitrile (318 g.), aniline (107 g.) and glacial acetic acid (69 g.) were heated together at 95°C for 45 minutes. Isopropanol (300 ml.) was then added and the mixture was cooled to 30°C; seeded; and treated with water (300 ml.) after crystallisation was obvious. Filtration gave β -anilino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=296 g. (after washing with water and isopropanol). 10

EXAMPLE 43

- 15 Aniline hydrochloride, from aniline (10 g.) and conc. hydrochloric acid (12 ml.), and β -morpholino- α -3,4,5-trimethoxybenzylacrylonitrile (30 g.) were reacted together in refluxing isopropanol (50 ml.) for 15 minutes. Water (25 ml.) was added and on cooling crystals of β -anilino- α -3,4,5-trimethoxybenzylacrylonitrile were obtained. Wt.=29 g. 15

EXAMPLE 44

- 20 β -Methoxy- α -3,4,5-trimethoxybenzylidenepropionitrile (53 g.), obtained according to method described in the specification of British Patent No. 957,797, morpholine (100 ml.) sodium methoxide (14 g.), and methanol (53 ml.) were heated together at 90°C for 15 minutes. The solvent was removed by evaporation in vacuo and the residue was poured into ice-water. The thick oil which separated was collected and washed by decantation and on treatment with ether gave crystalline β -morpholino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=53 g. 20

EXAMPLE 45

- 25 3,4,5-Trimethoxybenzaldehyde (25 g.), β -morpholinopropionitrile (20 g.), methanol (50 ml.), and sodium methoxide (1 g.) were heated together under reflux for 72 hours. Solvent was then removed in vacuo and the residue was crystallised from diethyl ether (100 ml.) to give β -morpholino- α -3,4,5-trimethoxybenzylidenepropionitrile. Wt.=18 g., m.p. 100.5—102°C (recrystallised from methanol). 25

EXAMPLE 46

- 35 3,4-Dimethoxybenzaldehyde (21 g.), β -morpholinopropionitrile (22 g.), sodium methylate (1 g.) and methanol (50 ml.) were heated together under reflux for 20 hours. Work-up as in Example 43 gave β -morpholino- α -3,4-dimethoxybenzylidenepropionitrile. Wt.=25 g., m.p. 95—97°C. (recrystallised from methanol). 35

EXAMPLE 47

- 40 The procedure of Example 45 using β -piperidinopropionitrile (20 g.) gave β -piperidino- α -3,4,5-trimethoxybenzylidenepropionitrile. Wt.=32 g., m.p. 60—62°C (recrystallised from isopropanol). 40

EXAMPLE 48

- 45 The procedure of Example 45 using β -pyrrolidinopropionitrile (20 g.) gave β -pyrrolidino- α -3,4,5-trimethoxybenzylidenepropionitrile as an oil. Wt. 37 g. 45

EXAMPLE 49

- 50 The procedure of Example 45 using β -dimethylaminopropionitrile (18 g.) gave β -dimethylamino- α -3,4,5-trimethoxybenzylidenepropionitrile. Wt.=20 g., m.p. 81—83°C (recrystallised from methanol). 50

EXAMPLE 50

- 55 The procedure of Example 45 using β -N-methylpiperazinopropionitrile (23 g.) gave β -N-methylpiperazino- α -3,4,5-trimethoxybenzylidenepropionitrile as a heavy oil, Wt.=40 g. 55

EXAMPLE 51

- 55 Piperonaldehyde (30 g.), β -morpholinopropionitrile (40 g.), methanol (75 ml.) 55

and sodium methoxide (1.5 g.) were heated together under reflux for 20 hours. Solvent was removed in vacuo and the residue recrystallised from ether, after treatment with aqueous sodium bisulphite, to give β -morpholino- α -piperonylidene propionitrile. Wt.=29 g., m.p. 80—85°C (recrystallised from methanol).

EXAMPLE 52

β -Morpholino- α -3,4,5-trimethoxybenzylidenepropionitrile (3 g.), dimethylsulphoxide (10 ml.) and sodium methoxide (0.1 g.) were heated together at 50—60°C for 10 minutes. Work-up gave crystalline β -morpholino- α -3,4,5-trimethoxybenzylacrylonitrile. m.p. 115—117°C.

EXAMPLE 53

The procedure of Example 52 was repeated using β -dimethylamino- α -3,4,5-trimethoxybenzylidenepropionitrile (4 g.) and on work-up gave β -dimethylamino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=3.2 g., m.p. 119—122°C (recrystallised from methanol).

EXAMPLE 54

The procedure of Example 52 was repeated using β -piperidino- α -3,4,5-trimethoxybenzylidenepropionitrile (3.5 g.) and on work-up gave β -piperidino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=2.7 g., m.p. 89—92°C.

EXAMPLE 55

β -Dimethylamino- α -3,4,5-trimethoxybenzylidenepropionitrile (2 g.), hexamethylphosphoramide (10 ml.), and sodium methoxide (0.05 g.) were heated together at 30°C. Conversion to β -dimethylamino- α -3,4,5-trimethoxybenzylacrylonitrile was complete in 1 minute and this compound was obtained on work-up. Wt.=1 g., m.p. 118—120°C (recrystallised from methanol).

EXAMPLE 56

β -Dimethylamino- α -3,4,5-trimethoxybenzylidenepropionitrile (2 g.), dimethylsulphoxide (10 ml.) and potassium *t*-butoxide (0.05 g.) at 30°C for 1 minute gave β -dimethylamino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=1 g., m.p. 119—121°C.

EXAMPLE 57

β -Dimethylamino- α -3,4,5-trimethoxybenzylidenepropionitrile (4 g.), hexamethylphosphoramide (10 ml.), and potassium *t*-butoxide (0.05 g.) at 30°C for 1—2 minutes gave β -dimethylamino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=3 g., m.p. 117—119°C.

EXAMPLE 58

β -Dimethylamino- α -3,4,5-trimethoxybenzylidenepropionitrile (2 g.), dimethylsulphoxide (10 ml.), and 3 drops of a saturated solution of potassium hydroxide in methanol at 40°C for 5 minutes gave β -dimethylamino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=1.3 g., m.p. 118—120°C.

EXAMPLE 59

The procedure as in Example 58 using hexamethylphosphoramide in place of dimethylsulphoxide in 2 minutes gave β -dimethylamino- α -3,4,5-trimethoxybenzylacrylonitrile. Wt.=1.8 g., m.p. 121—123°C.

EXAMPLE 60

The procedure as in Example 52 using β -pyrrolidino- α -3,4,5-trimethoxybenzylidenepropionitrile gave β -pyrrolidino- α -3,4,5-trimethoxybenzylacrylonitrile. m.p. 123—124°C.

EXAMPLE 61

The procedure as in Example 52 using β -morpholino- α -3,4-dimethoxybenzylidenepropionitrile gave β -morpholino- α -3,4-dimethoxyacrylonitrile. m.p. 127—129°C.

EXAMPLE 62

The procedure as in Example 52 using β -morpholino- α -piperonylidene propionitrile (5.0 g.) gave β -morpholino- α -piperonylacrylonitrile. Wt.=4.5 g., m.p. 82—84°C.

EXAMPLE 63

The procedure as in Example 53 using N,N-dimethylacetamide in place of dimethylsulphoxide gave β -dimethylamino- α -3,4,5-trimethoxybenzylacrylonitrile in 83% yield. m.p. 121—123°C.

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EXAMPLE 64

The procedure as in Example 55 using benzyltrimethylammonium hydroxide in place of sodium methoxide gave β -dimethylamino- α -3,4,5-trimethoxybenzylacrylonitrile in 86% yield. m.p. 122—123°C.

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EXAMPLE 65

The procedure as in Example 55, using β -morpholino-3,4-dimethoxybenzylidene-propionitrile (5 g.) gave β -morpholino-3,4-dimethoxybenzylacrylonitrile. Wt.=2.5 g., m.p. 127—129°C.

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EXAMPLE 66

β -Morpholino- α -3,4,5-trimethoxybenzylacrylonitrile (157 g.), was treated with conc. hydrochloric acid (75 ml.) in water (180 ml.) at 60°C for 15 minutes. The reaction mixture was cooled, extracted with chloroform (100 ml.; 75 ml.; 75 ml.), and the extracts were back-washed with water (75 ml.). Removal of solvent gave β -hydroxy- α -3,4,5-trimethoxybenzylacrylonitrile as a thick oil. Wt.=132 g. (theory).

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EXAMPLE 67

a). β -Anilino- α -3,4,5-trimethoxybenzylacrylonitrile (32 g.) and a solution of guanidine hydrochloride (19 g.) and sodium methoxide (13 g.) in denatured ethanol (100 ml.) were heated under reflux for 2½ hours the solvent (31 ml.) was boiled off and the mixture was cooled to 5°C. The resulting crystals of 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine were collected and washed with denatured ethanol and acetone. Wt.=27 g. (94%), m.p. 198—200°C.

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Using methanol in place of denatured ethanol gave 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine in 86% yield after 6 hours reflux; with isopropanol the reaction was over in 2 hours and the yield was 78%.

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b) The product from Example 24b was converted to 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine by the procedure of Example 67a in 4 hours in a 92% yield.

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c) The product from Example 24c was converted to 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine by the procedure of Example 67a in 3 hours in a yield greater than 90%.

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d) The product from Example 24d was converted to 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine by the procedure of Example 67a in 1.5 hours in a 95% yield.

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e) The product from Example 24e was converted to 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine by the procedure of Example 67a in several hours in a 72% yield.

f to j) The products from Examples 26b to f, were converted by the procedure of Example 67a, into

f) 2,4-Diamino-5-(3',4'-dichlorobenzyl) pyrimidine, m.p. 237—239°C.

g) 2,4-Diamino-5-(2'-iodobenzyl) pyrimidine, m.p. 265—267°.

h) 2,4-Diamino-5-(3'-iodobenzyl) pyrimidine, m.p. 220.5—222°.

i) 2,4-Diamino-5-(4'-iodobenzyl) pyrimidine, m.p. 246—248°.

j) and 2,4-diamino-5-(2'-bromobenzyl) pyrimidine, m.p. 248—250°.

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EXAMPLE 68

The procedure of Example 67 was repeated using β -anilino-5- α -3,4-dimethoxybenzylacrylonitrile (29.4 g.) and gave 2,4-diamino-5-(3',4'-dimethoxybenzyl)pyrimidine. Wt.=25.5 g., m.p. 230—233°C.

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EXAMPLE 69

The procedure of Example 67 was repeated using β -anilino-5- α -piperonylacrylonitrile (28 g.) and gave 2,4-diamino-5-piperonylpyrimidine. Wt.=22 g., m.p. 252—253°C (recrystallised from denatured ethanol).

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16	17	1,261,455	17
of di- 83%		EXAMPLE 70 The procedure of Example 67 was repeated using β -anilino- α -2-methyl-4,5-dimethoxybenzylacrylonitrile (16 g.) and after 18—20 hours reflux gave 2,4-diamino-5-(2'-methyl-4',5'-dimethoxybenzyl)pyrimidine. Wt.=11.5 g. (92%) m.p. 230—231°C.	
side in acrylo-	5	EXAMPLE 71 The procedure of Example 67 was repeated using β -anilino- α -3,4-dimethoxy-5-bromobenzylacrylonitrile (62 g.) and gave 2,4-diamino-5-(3',4'-dimethoxy-5'-bromobenzyl)pyrimidine. Wt.=38 g., m.p. 203.5—205°C.	5
idene- 2.5 g.,	10	EXAMPLE 72 The procedure of Example 67 was repeated using β -anilino- α - <i>p</i> -benzyloxybenzylacrylonitrile (25 g.) and gave after 4 hours reflux 2,4-diamino-5-(<i>p</i> -benzyloxybenzyl)pyrimidine. Wt.=20.5 g. This was converted to its acetate salt by treatment with acetic acid. Wt.=15 g.	10
with . The ml.), ve β - ory).	15	EXAMPLE 73 2,4-Diamino-5-(<i>p</i> -benzyloxybenzyl)pyrimidine acetate (4.6 g.) in methanol (200 ml.) was hydrogenated at low pressure over 5% Palladium/Carbon. The filtrate after removal of catalyst was evaporated and the resulting residue purified by dissolution in hot dilute acetic acid and re-precipitation with ammonium hydroxide to pH 9. Crystalline 2,4-diamino-5-(<i>p</i> -hydroxybenzyl)pyrimidine was collected and washed with water. Wt.=2.16 g., m.p. 300—303°C.	15
m of hanol d off 4',5'- l and	20	EXAMPLE 74 β -Morpholino- α -3,4,5-trimethoxybenzylacrylonitrile (32 g.), guanidine carbonate (34 g.) and dimethylsulphoxide (50 ml.) were heated together at 160°C for 1 hour with good stirring. The reaction mixture was cooled and poured into ice-water (200 ml.), and gave 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine which was collected and washed with water and acetone. Wt.=23.6 g. (80%) m.p. 196—198°C.	20
5'-tri- d the	25	EXAMPLE 75 The procedure of Example 74 was repeated using β -N-methylanilino- α -3,4,5-trimethoxybenzylacrylonitrile and gave 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine.	25
4',5'- 92%	30	EXAMPLE 76 The procedure of Example 74 was repeated using β -piperidino- α -3,4,5-trimethoxybenzylacrylonitrile and gave 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine.	30
4',5'- yield	35	EXAMPLE 77 The procedure of Example 74 was repeated using β -pyrrolidino- α -3,4,5-trimethoxybenzylacrylonitrile and gave 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine.	35
4',5'- 95%	40	EXAMPLE 78 The procedure of Example 74 was repeated using β -dimethylamino- α -3,4,5-trimethoxybenzylacrylonitrile and gave 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine.	40
4',5'- in a	45	EXAMPLE 79 The procedure of Example 74 was repeated using β -benzylamino- α -3,4,5-trimethoxybenzylacrylonitrile and gave 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine.	45
cedure	50	EXAMPLE 80 The procedure of Example 72 was repeated using β -morpholino- α -3,4-dimethoxybenzylacrylonitrile and gave 2,4-diamino-5-(3',4'-dimethoxybenzyl)pyrimidine.	50
oxy- imi-	55	EXAMPLE 81 The procedure of Example 74 was repeated using β -dimethylamino- α -3,4-dimethoxybenzylacrylonitrile and gave 2,4-diamino-5-(3',4'-dimethoxybenzyl)pyrimidine.	50

EXAMPLE 82

The procedure of Example 74 was repeated using β -morpholino- α -piperonylacrylonitrile and gave 2,4-diamino-5-piperonylpyrimidine.

EXAMPLE 83

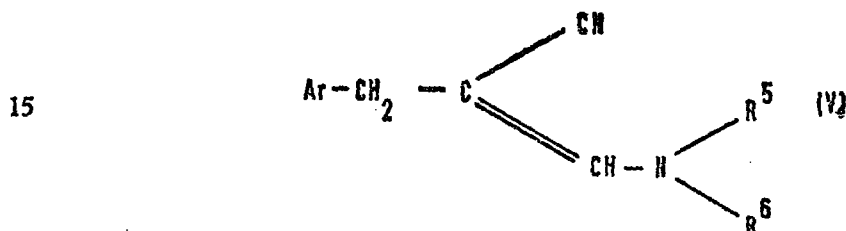
5 The procedure of Example 74 was repeated using β -morpholino- α -4,3-dimethoxy-5-bromobenzylacrylonitrile and gave 2,4-diamino-5-(3',4'-dimethoxy-5'-bromobenzyl)pyrimidine.

EXAMPLE 84

10 The procedure of Example 67 was repeated using β -methoxy- α -3,4,5-trimethoxybenzylacrylonitrile (54 g.) and after 20 hours reflux gave 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine. Wt. = 56 g., m.p. 198—200°C.

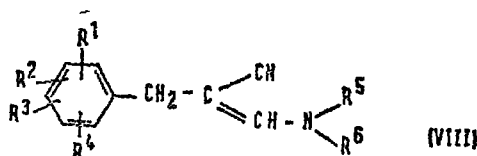
WHAT WE CLAIM IS:—

1. An *N*-substituted β -amino- α -benzylacrylonitrile compound according to formula (V),



in which Ar is an optionally substituted phenyl group, the group NR^5R^6 is an aliphatic, heterocyclic, or aromatic amino group and can have only one hydrogen atom for R^5 and R^6 , the compound being substantially free from contamination with the β -amino- α -benzylidenepropionitrile isomer, as hereinbefore defined.

20 2. An *N*-substituted β -amino- α -benzylacrylonitrile compound according to formula (VIII),



25 in which R^1 , R^2 , R^3 and R^4 are the same or different, and each is a hydrogen or halogen atom, an alkyl, alkoxy or benzyloxy group, or R^3 and R^4 taken together may be a methylenedioxy group when both R^1 and R^2 are hydrogen atoms, the group NR^5R^6 is an aliphatic, heterocyclic, or aromatic amino group and can have only one hydrogen atom for R^5 and R^6 , the compound being substantially free from contamination with the β -amino- α -benzylidenepropionitrile isomer, as hereinbefore defined.

30 3. A compound according to either of claims 1 and 2 in which the NR^5R^6 group is either (a) an anilino group optionally substituted in the phenyl ring, or (b) a secondary amino group other than the aforesaid anilino group, or (c) a tertiary amino group.

35 4. A compound according to any one of the preceding claims, in which the NR^5R^6 group comprises not more than 12 carbon atoms.

5. A compound according to any one of the preceding claims, in which the *para*-position of the phenyl group forming part of the benzyl group is substituted with a benzyloxy group.

40 6. A compound according to any one of claims 1 to 4, in which the *para*-position of the phenyl group forming part of the benzyl group is substituted with an alkoxy group.

7. A compound according to either of claims 5 and 6, in which either or both of the *meta*-positions in the phenyl group forming part of the benzyl group are substituted with an alkoxy group.



EXAMPLE 82

The procedure of Example 74 was repeated using β -morpholino- α -piperonylacrylonitrile and gave 2,4-diamino-5-piperonylpyrimidine.

EXAMPLE 83

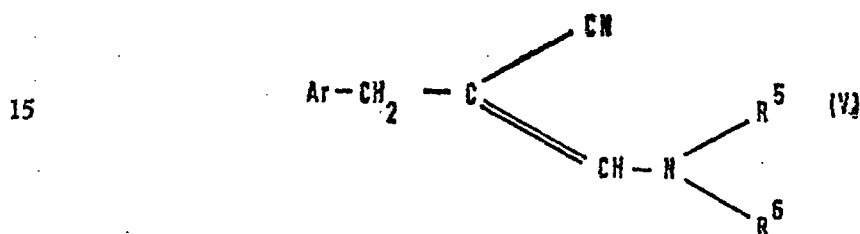
5 The procedure of Example 74 was repeated using β -morpholino- α -4,3-dimethoxy-5-bromobenzylacrylonitrile and gave 2,4-diamino-5-(3',4'-dimethoxy-5'-bromobenzyl)pyrimidine.

EXAMPLE 84

10 The procedure of Example 67 was repeated using β -methoxy- α -3,4,5-trimethoxybenzylacrylonitrile (54 g.) and after 20 hours reflux gave 2,4-diamino-5-(3',4',5'-trimethoxybenzyl)pyrimidine. Wt.=56 g., m.p. 198—200°C.

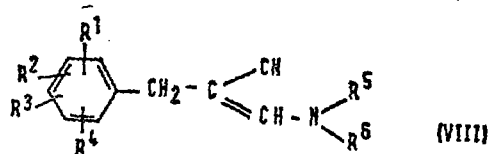
WHAT WE CLAIM IS:—

1. An *N*-substituted β -amino- α -benzylacrylonitrile compound according to formula (V),



in which Ar is an optionally substituted phenyl group, the group NR^5R^6 is an aliphatic, heterocyclic, or aromatic amino group and can have only one hydrogen atom for R^5 and R^6 , the compound being substantially free from contamination with the β -amino- α -benzylidenepropionitrile isomer, as hereinbefore defined.

20 2. An *N*-substituted β -amino- α -benzylacrylonitrile compound according to formula (VIII),



in which R^1 , R^2 , R^3 and R^4 are the same or different, and each is a hydrogen or halogen atom, an alkyl, alkoxy or benzyloxy group, or R^3 and R^4 taken together may be a methylenedioxy group when both R^1 and R^2 are hydrogen atoms, the group NR^5R^6 is an aliphatic, heterocyclic, or aromatic amino group and can have only one hydrogen atom for R^5 and R^6 , the compound being substantially free from contamination with the β -amino- α -benzylidenepropionitrile isomer, as hereinbefore defined.

30 3. A compound according to either of claims 1 and 2 in which the NR^5R^6 group is either (a) an anilino group optionally substituted in the phenyl ring, or (b) a secondary amino group other than the aforesaid anilino group, or (c) a tertiary amino group.

4. A compound according to any one of the preceding claims, in which the NR^5R^6 group comprises not more than 12 carbon atoms.

35 5. A compound according to any one of the preceding claims, in which the *para*-position of the phenyl group forming part of the benzyl group is substituted with a benzyloxy group.

40 6. A compound according to any one of claims 1 to 4, in which the *para*-position of the phenyl group forming part of the benzyl group is substituted with an alkoxy group.

7. A compound according to either of claims 5 and 6, in which either or both of the *meta*-positions in the phenyl group forming part of the benzyl group are substituted with an alkoxy group.

onyl-			8. A compound according to either of claims 6 and 7, in which each of the alkoxy groups is a methoxy group.	
neth-	5	5	9. A compound according to any one of claims 6 to 8, in which one of the <i>ortho</i> -positions of the phenyl group forming part of the benzyl group is substituted with an alkyl group having from 1 to 4 carbon atoms.	5
omo-			10. A compound according to claim 9, in which the lower alkyl group is a methyl group.	
neth-		10	11. A compound according to any one of claims 3 to 10, in which the NR ⁵ R ⁶ group is an anilino group, optionally substituted in the phenyl ring with one or more substituents selected from halogen atoms, alkyl, and alkoxy groups.	10
l',5'-	10		12. A compound according to claim 11, in which the anilino group is unsubstituted.	
for-		15	13. A compound according to claim 11, in which the phenyl group forming part of the benzyl group is 3,4,5-trimethoxy- or 3,4-dimethoxy-substituted, and the phenyl ring in the β -anilino group is substituted at the <i>para</i> -position with a chlorine atom, a methyl or methoxy group.	15
		20	14. β -Anilino- α -3,4,5-trimethoxybenzylacrylonitrile, substantially free from contamination with β -anilino- α -3,4,5-trimethoxybenzylidenepropionitrile, as hereinbefore defined.	
	15	20	15. β -Anilino- α -3,4-dimethoxybenzylacrylonitrile, substantially free from contamination with β -anilino- α -3,4-dimethoxybenzylidenepropionitrile, as hereinbefore defined.	20
		25	16. A compound according to any one of claims 3 to 10, in which the NR ⁵ R ⁶ group is a monoalkylamino, benzylamino or naphthylamino group.	25
		30	17. β -Benzylamino- α -3,4,5-trimethoxybenzyl acrylonitrile, substantially free from contamination with β -benzylamino- α -3,4,5-trimethoxybenzylidenepropionitrile, as hereinbefore defined.	30
an		30	18. A compound according to any one of claims 3 to 10, in which the NR ⁵ R ⁶ is a dialkylamino, morpholino, pyrrolidino, piperidino, <i>N</i> -methylanilino or a piperazino group such as the <i>N</i> -methylpiperazino group.	30
ogen			19. A compound according to claim 18, in which the NR ⁵ R ⁶ group is a morpholino group.	
with		35	20. β -Morpholino- α -3,4,5-trimethoxybenzylacrylonitrile substantially free from contamination with β -morpholino- α -3,4,5-trimethoxybenzylidenepropionitrile, as hereinbefore defined.	35
for-	20	40	21. β -Morpholino- α -3,4-dimethoxybenzylacrylonitrile substantially free from contamination with β -morpholino- α -3,4-dimethoxybenzylidene-propionitrile, as hereinbefore defined.	40
		45	22. A compound according to any one of the preceding claims, in which any contamination with the β -amino- α -benzylidenepropionitrile isomer is below 5%.	45
or			23. A compound according to claim 22, in which the contamination is below 2%.	
may			24. A compound according to claim 23, in which the contamination is less than 0.5%.	
oup	25		25. A compound according to claim 24 in which the contamination is 0.33% or less.	45
one		50	26. A method of preparing a compound according to formula (V) or (VIII) as defined in any one of claims 1 to 21, which comprises reacting the corresponding benzaldehyde with corresponding β -amino-propionitrile in the presence of a base in a polar aprotic solvent compatible with and dissolving both reactants.	50
na-		55	27. A method according to claim 26, wherein the reaction is carried out in the presence of an effective quantity of less than 0.3 molar equivalent of the base, at a temperature above 60°C.	55
oup	30		28. A method according to claim 27 wherein the temperature is in the range of from 90°C to 130°C.	
a			29. A method according to claim 26 wherein the reaction is carried out in the presence of 0.5 to 2 molar equivalents of the base at a temperature between room temperature and 60°C.	
ino		60	30. A method according to any one of claims 26 to 29, wherein the polar aprotic solvent is dimethylsulphoxide.	60
the			31. A method according to any one of the claims 26 to 30, wherein the anion of the base is a alkoxide anion having from 1 to 4 carbon atoms.	
ra-	35		32. A method according to claim 31, wherein the alkoxide anion is the methoxide anion.	
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33. A method according to claim 31, wherein the alkoxide anion is the tertiary butoxide anion.

34. A method according to any one of claims 26 to 33, wherein the nitrile is β -anilino-propionitrile.

5 35. A method according to any one of claims 26 to 33, wherein the nitrile is β -morpholino-propionitrile. 5 5

36. A method according to any one of claims 26 to 35, wherein the aldehyde is an optionally further substituted 3,4-dimethoxybenzaldehyde.

10 37. A method according to claim 36, wherein the reactant is 3,4,5-trimethoxybenzaldehyde. 10 10

38. A method according to claim 36, wherein the reactant is 3,4-dimethoxybenzaldehyde.

39. A method according to claim 26 substantially as described in any one of Examples 1 to 23.

15 40. A method of preparing a compound according to formula (V) or (VIII) as defined in any one of claims 1 to 21, which comprises reacting a corresponding (β -hydroxy- β -phenyl-ethyl) methyl sulphone or sulfoxide with the corresponding β -aminopropionitrile. 15 15

41. A method according to claim 40, wherein the reaction is carried out in the presence of a base in a polar non-aqueous solvent compatible with a dissolving both reactants. 20 20

42. A method according to claim 40, wherein the anion of the base is a methoxide or tertiary butoxide anion and the solvent is dimethylsulphoxide.

43. A method according to either of claims 41 and 42, wherein the reaction is carried out at elevated temperatures above 30°C. 25 25

44. A method according to any one of claims 40 to 43, wherein β -anilino-propionitrile is used as a reactant.

45. A method according to any one of claims 40 to 44, wherein the (β -hydroxy- β -phenyl-ethyl) methyl sulphone or sulfoxide reactant carries an alkoxy substitution on the *para* and/or *meta*-positions. 30 30

46. A method according to claim 30, substantially as described in any one of Examples 26 to 39.

47. A method of preparing a compound according to formula (V) or (VIII), as defined in any one of claims 1 to 21, which comprises reacting the corresponding β -hydroxy- α -benzylacrylonitrile with the appropriate amine. 35 35

48. A method according to claim 47, wherein the reaction is carried out in a non-aqueous solvent.

49. A method according to claim 48, wherein the solvent is an alkanol, for example ethanol.

40 50. A method according to claim 48, wherein the solvent is benzene. 40 40

51. A method according to any one of claims 47 to 50, wherein the reaction is carried out at an elevated temperature, preferably refluxing temperatures.

52. A method according to claim 47, substantially as described in either of Examples 24 and 25.

45 53. A method of preparing a compound according to formula (V) or (VIII), in which the NR^aR^b group is an anilino group optionally substituted in the phenyl ring, which comprises reacting the corresponding benzaldehyde with the corresponding β -anilino-propionitrile. 45 45

54. A method according to claim 53, wherein the reaction is carried out in the presence of a base in a polar non-aprotic solvent. 50 50

55. A method according to claim 54, wherein the organic solvent is a lower alkanol, having from 1 to 4 carbon atoms.

56. A method according to claim 55, wherein the alkanol is methanol.

57. A method according to any one of claims 54 to 56, wherein more than 1 equivalent of the base is used at elevated temperatures between 40 and 80°C. 55 55

58. A method according to claim 53, substantially as described in either of Examples 40 and 41.

60 59. A method of preparing a compound according to formula (V) or (VIII), in which the NR^aR^b group is an anilino group optionally substituted in the phenyl ring, which comprises reacting the corresponding aniline in the form of an acid addition salt with a compound of formula (V) or (VIII), as defined in either of claims 1 and 2, carrying an amino substituent group NR^aR^b , which has, as a free amine, a pKa value higher by at least three, for example at least four, units than that of the aniline used for the reaction. 60 60





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60. A method according to claim 59, wherein the reaction is carried out in a polar non-aqueous solvent.

61. A method according to claim 60, wherein the polar solvent is ethanol or glacial acetic acid and the reaction is carried out at elevated temperatures.

62. A method according to any one of claims 59 to 61, wherein an aniline salt is reacted with a β -morpholino- α -benzylacrylonitrile.

63. A method according to any one of claims 59 to 62, wherein the salt is the hydrochloride or the acetate.

64. A method according to claim 59, substantially as described in either of Examples 42 or 43.

65. A method of preparing a compound according to formula (V) or (VIII), in which the NR^2R^6 group is a secondary amino group is other than an anilino group or is a tertiary amino group, which comprises reacting the corresponding β -alkoxy- α -benzylidene propionitrile with an excess of the appropriate primary amine, other than aniline, or secondary amine in the presence of a base in an alkanol.

66. A method according to claim 65, wherein the alkanol is methanol.

67. A method according to either of claims 65 and 66, wherein the anion of the base is an alkoxide anion, such as the methoxide anion.

68. A method according to any one of claims 65 to 67, wherein a β -methoxy- α -benzylidenepropionitrile is reacted with morpholine in the presence of about one equivalent of a methoxide base.

69. A method according to claim 65, substantially as described in Example 44.

70. A method of preparing a compound according to formula (V) or (VIII), in which the NR^2R^6 group is a secondary amino group other than an anilino group or is a tertiary amino group, which comprises isomerizing the corresponding β -amino- α -benzylidene-propionitrile isomer with a base in a polar aprotic solvent.

71. A method according to claim 71, wherein the molar concentration of the base is from 0.01 mole to 1 mole.

72. A method according to claim 72, wherein the molar concentration of the base is about 0.1 mole.

73. A method according to any one of claims 70 to 72, wherein the anion of the base is the methoxide anion.

74. A method according to any one of claims 70 to 72, wherein the anion of the base is the *t*-butoxide anion.

75. A method according to any one of claims 70 to 74, wherein the solvent is dimethylsulphoxide.

76. A method according to any one of claims 70 to 74, wherein the solvent is hexamethylphosphoramide.

77. A method according to any one of claims 70 to 76, wherein the NR^2R^6 group is β -morpholino.

78. A method according to any one of claims 70 to 77, wherein the α -benzylidene group is an optionally further substituted 3,4-dimethoxy-benzylidene group.

79. A method according to claim 70, substantially as described in any one of Examples 52 to 65.

80. A method according to any one of claims 70 to 79, wherein the α -amino- α -benzylidene-propionitrile is prepared by reacting the corresponding benzaldehyde with the corresponding β -amino-propionitrile in the presence of an effective amount of less than 0.3 molar equivalent of a base in an alkanolic solvent.

81. A method according to claim 80, including a step substantially as described in any one of Examples 45 to 51.

82. An *N*-substituted- β -amino- α -benzylacrylonitrile according to formula (V) or (VIII), as hereinbefore defined, whenever prepared by a method according to any one of claims 26 to 81.

83. A method of preparing a 2,4-diamino-5-benzylpyrimidine, which comprises reacting a β -amino- α -benzylacrylonitrile compound, as claimed in any one of claims 1 to 25 and 82 with guanidine.

84. A method of preparing a 2,4-diamino-5-benzylpyrimidine of formula (IX) herein, wherein R^1 , R^2 , R^3 and R^4 are as defined in formula (VIII), which comprises reacting a corresponding β -amino- α -benzylacrylonitrile of formula (VIII), as defined in any one of claims 2 to 25, and 82 with guanidine.

85. A method according to either of claims 83 and 84, wherein the *para*-position of the benzyl group is substituted with an alkoxy, benzyloxy or hydroxy group.

86. A method according to claim 85, wherein either or both of the *meta*-positions of the benzyl group are substituted with an alkoxy group.

87. A method according to either of claims 85 and 86, wherein each of the alkoxy groups is a methoxy group.
- 5 88. A method according to any one of claims 85 to 87, wherein the *ortho*-position of the benzyl group is substituted with a alkyl group, having from 1 to 4 carbon atoms, preferably a methyl group. 5
89. A method according to any one of claims 83 to 88, wherein the amino group of the β -amino- α -benzylacrylonitrile is an anilino group.
90. A method according to claim 89, wherein the reaction is carried out in a alkanol having from 1 to 4 carbon atoms at elevated temperatures. 10
91. A method according to claim 90, wherein the alkanol is ethanol. 10
92. A method according to either of claims 90 and 91, wherein the temperature is the reflux temperature of the mixture.
93. A method according to any one of claims 83 to 92, wherein β -anilino- α -3,4,5-trimethoxybenzyl acrylonitrile is reacted with guanidine to obtain trimethoprim. 15
94. A method according to any one of claims 83 to 88, wherein the amino group of the β -amino- α -benzylacrylonitrile is other than anilino, and this compound is reacted with guanidine in the form of the carbonate in a polar aprotic solvent. 15
95. A method according to claim 94, wherein the polar aprotic solvent is dimethylsulphoxide.
- 20 96. A method according to either of claims 94 to 95, wherein the reaction is carried out at refluxing temperatures. 20
97. A method according to any one of claims 94, 96, wherein the nitrile is β -morpholino-3,4,5-trimethoxybenzylacrylonitrile to obtain trimethoprim.
- 25 98. A method according to any one of claims 94 to 96, wherein the nitrile is β -morpholino-3,4-dimethoxybenzylacrylonitrile to obtain diaveridine. 25
99. A method according to claim 83, substantially as described in any one of Examples 67 to 84.
100. 2,4-Diamino-5-benzylpyrimidines, whenever prepared by a method claimed in any one of claims 83 to 99.
- 30 101. A method of preparing a β -hydroxy- α -benzylacrylonitrile corresponding to a compound of formula (V) or (VIII), as defined in any one of claims 1 to 25, having the NR^2R^3 replaced by a hydroxy group, which comprises hydrolysing a β -amino- α -benzylacrylonitrile of formula (V) or (VIII), as defined in any one of claims 1 to 21, with an acid in an aqueous medium. 30
- 35 102. A method according to claim 101, wherein β -morpholino- α -benzylacrylonitrile is hydrolysed with a dilute aqueous solution of a mineral acid. 35
103. A method according to claim 101, substantially as described in Example 66.

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