PATENT SPECIFICATION

NO DRAWINGS

957,797

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Date of filing Complete Specification (under Section 3 (3) of the Patents Act, 1949): July 29, 1960.

Application Date: Sept. 3, 1959. *No. 30102/59.*

Application Date Nov. 20, 1959. *No. 39560/59.*

Application Date: July 11, 1960. *No. 24101/60.*

Complete Specification Published: May 13, 1964.

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Index at acceptance:—C2 C(1F2A2, 1F2C4, 1F2D3, 1F4A2, 1F4C4, 1F4D2, 1F4F3, 1H1A1, 1H1C3, 2A3, 2A10, 2B3A4, 2B3B, 2B3D, 2B3G5, 2B18, 2B20, 2D24, 2R18)

International Classification:—C 07 d

COMPLETE SPECIFICATION

Method for making 2,4-Diamino-5-Arylmethylpyrimidines and Intermediates therefor

We, THE WELLCOME FOUNDATION LIMITED, a Company incorporated in England, of 183—193 Euston Road, London, N.W.1, do hereby declare the invention, a communication from Burroughs Wellcome & Co. (U.S.A.) Inc., of 1, Scarsdale Road, Tuckahoe 7, New York, United States of America, 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:—

The class of 2,4 - diamino - 5 - arylmethylpyrimidines described in United States specification 2,624,732 contains many compounds with chemotherapeutic activity. Certain compounds described and claimed in United States specification 2,579,259 and British specification 687,032 have antimalarial activity, while others described and claimed in United States specifications 2,658,897 and 2,909,522 and British specifications 734,801, 875,562 and 920,412 have high antibacterial activity. In general, the biologically active compounds are 2,4 - diamino - 5 - benzylpyrimidines in which the benzene ring is substituted with alkoxy (including methylenedioxy), alkyl, amino, dialkylamino, nitro (introduced by nitration as a final step), and/or halogen or with .CH : CH.CH : CH. to form a naphthalene ring. In particular, the 2,4 - diamino - 5-(3,4 - dialkoxybenzyl)pyrimidines, with or without further substituents in the benzene ring, have very high antibacterial activity, especially against *Proteus vulgaris, Streptococcus pyogenes,* and *Staphylococcus aureus* including strains resistant to antibiotics. Such compounds exhibit synergism in combination with sulphanilamides, and as described in United States specification 2,823,160 these combinations are effective against the parasitic protozoon *Eimeria tenella,* the causative organism of coccidiosis in chickens.

The exploitation of these compounds has been hindered by the cost of manufacture. They have hitherto been made from the corresponding aromatic aldehyde in seven stages: (a) the aldehyde is condensed with malonic acid, (b) the resulting β-arylacrylic acid is esterified, (c) the ester is reduced, (d) the resulting β-arylpropionic ester is condensed with a formic ester, (e) the resulting α-formyl ester is condensed with guanidine, (f) the resulting 2 - amino - 4 - hydroxy - 5 - arylmethylpyrimidine is chlorinated, and (g) the 2 - amino - 4 - chloro - 5 - arylmethylpyrimidine is ~~animated~~ aminated to give the final product. Although steps (a) to (c) give excellent yields, all of steps (d) to (g) are somewhat unsatisfactory. The large number of steps and the multiplication of poor yields in the last four makes the final products too expensive for many potential uses; for example, the over-all yield of 2,4 - diamino - 5 - (3,4 - dimethoxybenzyl)pyrimidine by this process is only 5—10%.

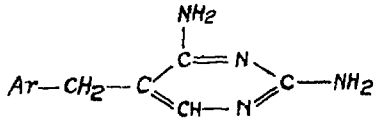
It has now been found that a 2,4 - diamino-5 - arylmethylpyrimidine II can readily be made in good over-all yield, 25—30% in some instances and as high as 60% in others, by condensing an aromatic aldehyde Ar.CHO with a β-substituted propiononitrile $Y.CH_2.CH_2.CN$ to give as an intermediate

[*Price 4s. 6d.*]

product a substance consisting of one or more nitriles Ia and Ib, followed by condensation of this substance with guanidine.

$$Ar.CH:C(CN).CH_2.Z \quad \text{(Ia)}$$

$$Ar.CH_2.C(CN):CH.Z \quad \text{(Ib)}$$



(II)

In these formulae Ar is a phenyl group optionally substituted with alkoxy, alkyl, amino, dialkylamino, and/or halogen or with .CH:CH.CH:CH., and Y is an electrophilic group such as an ether, thioether or tertiary amino group and is preferably an alkoxy group. In condensations with the β-substituted propiononitrile in an alcoholic solution, exchange of electrophilic group occurs and Z is largely the alkoxy group corresponding to the solvent alcohol; otherwise it is the group Y. When Y is an alkylthio or dialkylamino group, this exchange is partial. When Y is an alkoxy group different from that derived from the solvent alcohol, exchange is not demonstrably complete but is very extensive. As Z is eliminated during the condensation with guanidine, its identity within the limits specified is of little practical importance.

The reaction leading to the intermediate product Ia and Ib is carried out in the presence of a strongly basic catalyst such as alkoxide or amide anion. The use of amide anion, for example as sodamide, requires a non-hydroxylic solvent. In practice, the reaction is best carried out in solution in a lower alcohol, using as catalyst the sodium derivative of that alcohol. When working in alcoholic solution, it is possible to employ acrylonitrile, (or a precursor such as a β-halogenopropiononitrile which gives acrylonitrile by the loss of the elements of hydrogen halide), because acrylonitrile adds the elements of the solvent alcohol and forms the corresponding β-alkoxypropiononitrile *in situ*.

During the reaction leading to the intermediate product Ia and Ib, water is produced. Generally, it is best to remove it, for example by azeotropic distillation or by adding a reagent such as magnesium methoxide.

The intermediate product is in general a mixture of isomers Ia and Ib (each of which may exist in geometrically isomeric forms). If desired, the intermediate product can be purified from other materials by distillation in a good vacuum. In certain instances, crystalline substances have been separated and shown to have the structure Ia.

The intermediate products Ia are new substances, and form one aspect of this invention.

The condensation of the intermediate product Ia and Ib with guanidine is carried out in solution in any lower alcohol, preferably using 2 to 3 equivalents of guanidine. Where Ar has an alkoxy substituent (RO) at the 2 or 4 position, there is a distinct advantage in using the corresponding alcohol ROH as solvent. For making 2,4 - diamino - 5-(3,4 - dimethoxybenzyl)pyrimidine and 2,4-diamino - 5 - (3,4,5 - trimethoxybenzyl)-pyrimidine, which have especially desirable biological activity, it is therefore preferable to use methanol as solvent. This can be employed at reflux temperature, or at a slightly lower temperature (such as 56°C) for a longer time. If the reaction mixture is refluxed, stirring is desirable to prevent bumping, as many of the pyrimidine products II crystallise out during the reaction.

In instances where the isomer Ia of the intermediate product has been separated, substantially the same result on condensation with guanidine is obtained with the pure isomer as with the crude mixture of isomers. The concentration of the intermediate product is advantageously 0.5 to 1.0 molar.

The yield of pyrimidine II from the condensation of the intermediate product Ia and Ib with guanidine depends on the nature of Ar, being as high as 80% in some instances, and about 40—45% in others. Loss in the latter is apparently due to a concurrent polymerisation. This seems to be unavoidable, as it involves substituents in Ar that are at times desirable.

It is possible to conduct the conversion of the aromatic aldehyde to the pyrimidine II in one operation. That is to say, guanidine base is added directly to the unpurified reaction mixture containing the intermediate product Ia and Ib, and only the final pyrimidine product II is isolated. The yield is about the same as the over-all yield achieved in the separate steps, and this simplification brings the considerable practical advantage of greater ease of working in large-scale manufacture. In such an operation, 2,4 - diamino-5 - (3,4 - dimethoxybenzyl)pyrimidine can be prepared in greater than 30% yield from veratric aldehyde.

The method described above for making the pyrimidines II and the pyrimidines II when thus made, either from the isolated intermediate product Ia and Ib (or one isomer) or in one operation from the aromatic aldehyde, form other aspects of this invention.

The following examples illustrate the invention. Temperatures are given in degrees Celsius and pressures in millimetres of mercury. The intermediate products, mixtures of Ia and Ib, are called "-alnitriles" after the

aromatic aldehyde used. The solvent described as "alcohol" is anhydrous ethanol containing 5% methanol.

EXAMPLE 1

33 g. Veratraldehyde and 20 g. β-ethoxypropiononitrile were added to a solution of 2.8 g. sodium methoxide in 140 ml. anhydrous alcohol. The solution was distilled slowly removing about 40 ml. distillate each half-hour and replacing that amount of fresh anhydrous alcohol. After two hours the solution was concentrated *in vacuo* to a thick syrup and diluted with 500 ml. cold water. The veratralnitrile was extracted with ether. The ethereal extract was washed with water until the washings were neutral, and dried over sodium sulphate. The ether was evaporated and the residue was distilled at 0.45 mm. 37.7 g. β-Ethoxy veratralnitrile (76% yield) was obtained at 155—175°, m.p. 55—57° when recrystallised from ethanol. Its solution in alcohol had ultraviolet absorption maxima at 324 mμ (e=13600), 295 mμ (e=10900) and 238 mμ (e=10000), indicating the presence of the chromophore NC.C=C.R and the structure α-veratrylidene - β - ethoxypropiononitrile.

14.25 g. Guanidine hydrochloride dissolved in 25 ml. methanol was added to 8.1 g. sodium methoxide dissolved in 35 ml. methanol. Sodium chloride was filtered off and washed with 30 ml. methanol. The filtrate and washes were added to 12.35 g. α-veratrylidene-β-ethoxypropiononitrile and the solution was refluxed for five hours. The slurry was chilled in an icebath and the solid filtered off and washed with cold methanol. The filtrate and washes were reduced by boiling to 60 ml. and then refluxed for 18 hours. The slurry was chilled in an icebath, and the solid filtered off, washed with cold methanol and added to the first crop. The crude 2,4 - diamino - 5-(3,4 - dimethoxybenzyl)pyrimidine was dissolved in 50 ml. 10% acetic acid, filtered, and reprecipitated by adding ammonia to bring the pH to 8.5. The reprecipitated pyrimidine was washed with water and then with 50% aqueous acetone, and dried at 100° to give 4.4 g. (34% yield).

The use of β-methoxy, β-isopropoxy or β-n-butoxypropiononitrile dissolved in the corresponding alcohol gave the homologous β-alkoxy veratralnitrile. If the solvent was ethanolic, the veratralnitrile was not homogeneous but contained some β-ethoxy compound. Such mixtures could not be crystallised but were satisfactory for the cyclisation with guanidine.

Similar mixtures were obtained by the use of β-ethoxypropiononitrile dissolved in an alcohol other than ethanol. 6 g. Sodium was dissolved in 350 ml. methanol, and 82.5 g. veratraldehyde and 49.5 g. β-ethoxypropiononitrile were added. The mixture was refluxed for 24 hours and the product worked up using the procedure described in Example 8 to give 48 g. veratralnitrile (38% yield), readily cyclisable with guanidine. The use of n-propanol in place of methanol gave a 20% yield of veratralnitrile, and the use of n-butanol in place of methanol (reflux time 4 hours) gave a 20% yield of veratralnitrile, satisfactory in subsequent condensation with guanidine.

For conversion to the higher-melting β-methoxy compound, 4 g. α-veratrylidene-β-ethoxypropiononitrile, m.p. 57°, was dissolved in 50 ml. methanol in which 0.1 g. sodium had already been dissolved. The solution was refluxed for one hour, cooled, and seeded with the β-methoxy veratralnitrile. The following morning the separated solid was filtered off and washed with ice-cold methanol in which most dissolved. The remaining solid (0.7 g.) melted at 45—48°. The mother-liquor and washings were evaporated to about 25 ml. and refluxed for 1.5 hours. After standing overnight solid was filtered off and washed as before; the residue (0.2 g.) melted at 61—69°. The filtrate was again evaporated to small volume and refluxed for 1.5 hours, and yielded on cooling 1.3 g. solid, m.p. 73°, identical with the α-veratrylidene-β-methoxypropiononitrile described in Example 16.

In the condensation of β-ethoxy veratralnitrile with guanidine, it was possible to replace excess guanidine by sodium methoxide. 12.5 g. β-Ethoxy veratralnitrile was mixed with 2.95 g. guanidine and 5.4 g. sodium methoxide in 100 ml. methanol and the mixture refluxed for 24 hours. The solid formed was filtered off and washed with a little methanol. The mother liquors and washings were concentrated to about 50 ml. and refluxed overnight. A second crop of solid was obtained which was washed with aqueous acetone. The total yield was 3 g. 2,4 - diamino - 5 - (3,4-dimethoxybenzyl)pyrimidine (23% yield), m.p. 228°.

It was also possible to use guanidine carbonate instead of the free base. 12.5 g. β-Ethoxy veratralnitrile was stirred with 34 g. guanidine carbonate in 100 ml. methanol and refluxed for 24 hours. The solid was filtered off and washed with a little methanol. The filtrate was concentrated to 40 ml. and further treated with 17 g. guanidine carbonate. The ~~solid~~ solid obtained was filtered off, combined with the first crop, treated with 50 ml. aqueous acetone, and dried to give 1.4 g. 2,4-diamino-5 - (3,4 - dimethoxybenzyl)pyrimidine (11% yield), m.p. 223°.

EXAMPLE 2

588 g. 3,4,5-Trimethoxybenzaldehyde and 297 g. β-ethoxypropiononitrile were added to a solution of 42 g. sodium methoxide in 2100 ml. anhydrous alcohol. The solution was distilled slowly removing 425 ml. distillate each half-hour and replacing that amount of fresh anhydrous alcohol. After two hours the solu-

tion was concentrated *in vacuo* to a syrup and stirred with 2000 ml. water at 0°. Acetic acid was added to bring the pH to 6—7, and then ammonia was added bringing the pH to 8.5. The oily product became very stiff. The aqueous layer was decanted and the product washed with 2000 ml. water at 0°. The partly-crystalline β-ethoxy 3,4,5-trimethoxybenzalnitrile was dried under reduced pressure at 50° to give 721 g. (87% yield), satisfactory for cyclisation with guanidine. α - 3,4,5-Trimethoxybenzylidene - β - ethoxypropiononitrile was isolated as a solid that melted at 74—75° when ~~crystallised~~ once from ~~methanol;~~ recrystallised ethanol; further recrystallisation from methanol raised the melting point to 79—80°.

740 g. Guanidine hydrochloride dissolved in 1500 ml. methanol was added to 420 g. sodium methoxide dissolved in 2700 ml. methanol. Sodium chloride was filtered off and washed with 450 ml. methanol. The filtrate and washes were added to 721 g. α-3,4,5-trimethoxybenzylidene - β - ethoxypropiononitrile, and the solution was refluxed for two hours. After standing overnight at 3°, the mixture was seeded with 2,4 - diamino - 5-(3,4,5 - trimethoxybenzyl)pyrimidine and yielded 120 g. crude product. The filtrate was concentrated by boiling off 1500 ml. at atmospheric pressure and then refluxed, having a total of four hours at boiling temperature. On standing overnight at 3° with added seed, a second crop of 100 g. crude product was obtained. The filtrate was further concentrated by boiling off another 1000 ml. and refluxed for a total of three hours. After two days at 3° a third crop of 55 g. crude product was recovered. 284 g. Crude product was recrystallised from 2000 ml. hot 80% alcohol to give 214 g. 2,4 - diamino - 5 - (3,4,5-trimethoxybenzyl)pyrimidine (28% yield) as pale yellow crystals, m.p. 195—197°.

Similar condensations in ethanol using β-methoxy or β - isopropoxypropiononitrile afforded oily products, but these gave satisfactory yields of 2,4 - diamino - 5 - (3,4,5-trimethoxybenzyl)pyrimidine when reacted with guanidine.

For conversion to the β-methoxy compound, 3.5 g. α - 3,4,5 - trimethoxybenzylidene - β-ethoxypropiononitrile, m.p. 79—80°, was dissolved in 20 ml. methanol in which 0.1 g. sodium had been dissolved. The solution was refluxed 4 hours, and cooled. The solid that separated was recrystallised twice from methanol to give 1.5 g. α - 3,4,5 - trimethoxybenzylidene - β - methoxypropiononitrile, m.p. 85°. The mixed m.p. with the starting compound showed a large depression. The product had absorption maxima at 232 mμ (e=15140) and 308 mμ (e=15060) and a minimum at 260 mμ (e=2760).

Example 3

367 g. 3 - Methoxy - 4 - n - butoxy - 5-bromobenzaldehyde was reacted with 160 g. β-ethoxypropiononitrile in a solution of 18 g. sodium methoxide in 895 ml. alcohol, using the procedure of Example 1. 374 g. β-Ethoxy 3 - methoxy - 4 - n - butoxy - 5 - bromobenzalnitrile (80% yield if pure) was obtained as an undistilled oil.

Guanidine (from 285 g. hydrochloride) dissolved in 1650 ml. methanol was added to 351 g. β-ethoxy 3 - methoxy - 4 - n - butoxy-5 - bromobenzalnitrile. The mixture was refluxed for 5 hours and then let stand at 2° for 2 days. A crop of 10 g. crystals was filtered off, and the mother liquor and washes were concentrated by boiling off 500 ml. methanol. The solution was cooled for one hour in an ice-acetone bath to give a second crop of 32 g. crystals. The mother liquor and washes were concentrated by boiling off 500 ml. methanol and chilled, but no solid appeared. The solution was diluted with 250 ml. methanol and refluxed for four hours. It was concentrated under reduced pressure to a thick syrup, and was then diluted with 750 ml. alcohol and chilled in an icebath giving a third crop of about 75 g. The mother liquor was concentrated under reduced pressure and poured into 2000 ml. ether. The supernatant was decanted, 1000 ml. ether was added together with filter-aid, and the combined ether solution was filtered through filter-aid. The filtrate was concentrated under reduced pressure to a thick syrup which was dissolved in alcohol and yielded a fourth crop of crystals on chilling. The four crops were combined, dissolved in 2800 ml. hot water containing 280 ml. acetic acid and treated with charcoal. The filtrate was chilled overnight at 2°, and the solid was filtered off, washed with water, and stirred with 700 ml. water bringing the pH to 11.0 with ammonia. The mixture was heated to 70°, and chilled to give 54 g. 2,4-diamino - 5 - (3 - methoxy - 4 - n - butoxy-5 - bromobenzyl)pyrimidine, m.p. 178—180°.

Example 4

70 g. 4-Chlorobenzaldehyde was reacted with 50 g. β-ethoxypropiononitrile in a solution of 7 g. sodium methoxide in 350 ml. alcohol, using the procedure of Example 1. 83 g. crude β-ethoxy 4-chlorobenzalnitrile (75% yield) was obtained as an undistilled oil which lacked the strong characteristic odours of 4-chlorobenzaldehyde and β-ethoxypropiononitrile.

Guanidine (from 57 g. hydrochloride) dissolved in 360 ml. methanol was added to 44 g. β-ethoxy 4-chlorobenzalnitrile. The mixture was refluxed for 2.5 hours and then chilled in an icebath for an hour. The precipitate was filtered and washed with methanol. The filtrate and washes were boiled at atmospheric pressure to 250 ml. total volume and then refluxed for a total of 2 hours. The solution was chilled to give a second crop

of crystals. The filtrate and washings were concentrated under reduced pressure to a thick syrup which was diluted with alcohol. A third crop precipitated, and a fourth crop was obtained from the filtrate after standing overnight at 2°. The four crops were combined, slurried and washed with ice-cold alcohol to remove much colour, and dissolved in 175 ml. warm 10% acetic acid. After charcoal treatment, the light green solution yielded on chilling crystals of 2,4 - diamino - 5 - (4 - chlorobenzyl)pyrimidine acetate which contained most of the colour. The acetate salt was slurried in water at 60° and brought to pH 8.0 with ammonia. After chilling, the solid was filtered off and slurried in acetone to remove much colour and giving 9 g. 2,4-diamino - 5 - (4 - chlorobenzyl)pyrimidine, m.p. 215—217°. The acetone was concentrated to a sludge which was redissolved in a minimum of boiling acetone to give 1.0 g. crystals, m.p. 218—220°. The total yield was thus 10 g. (21%).

EXAMPLE 5

20 g. 3-Ethoxybenzaldehyde and 20 ml. β-ethoxypropiononitrile were added to 160 ml. absolute ethanol in which 2.5 g. sodium had been dissolved. The solution was heated under a fractionating column. 40 ml. Benzene was added, and about 100 ml. distillate was taken off slowly over a period of 8 hours. The solution was then allowed to stand overnight, concentrated rapidly, and then partitioned between ether and water. The ethereal layer was washed with bisulphite solution, dried briefly over calcium chloride, and evaporated. The oily residue was distilled at 1 mm. to give 70% yield of the β-ethoxy 3-ethoxybenzalnitrile as an oil boiling at 140—165°, probably a mixture of isomers.

11 g. β-Ethoxy 3-ethoxybenzalnitrile was treated with a guanidine solution in methanol as in previous examples. The mixture was refluxed for 48 hours (a shorter time gave an inferior yield). On cooling, a solid separated. This was filtered off and washed successively with methanol, water, acetone and ether. This crop of the product weighted 8.3 g.; a further crop of 0.7 g. was obtained from the mother liquors (75% yield). For analysis, it was recrystallised from methanol and then melted at 174°. It had the correct composition for 2,4 - diamino - 5 - (3 - ethoxybenzyl)-pyrimidine.

EXAMPLE 6

12 ml. β-Ethoxypropiononitrile was condensed with 18.5 g. 3-methoxy-4-s-butoxybenzaldehyde, using the method of Example 5, to give the β-ethoxy 3-methoxy-4-s-butoxybenzalnitrile, an oil purified by chromatography.

β - Ethoxy 3 - methoxy - 4 - s - butoxybenzalnitrile was reacted with guanidine, using the procedure of Example 9, to give 2,4-diamino - 5 - (3 - methoxy - 4 - s - butoxybenzyl)pyrimidine, m.p. 181°.

EXAMPLE 7

12 g. β-Ethoxypropiononitrile was condensed with 21 g. 3-methoxy-4-n-octyloxybenzaldehyde, using the method of Example 5, to give the β-ethoxy 3-methoxy-4-n-octyloxybenzalnitrile as an oil that was distilled at 2—6 μ, boiling over the range 130—140°.

β - Ethoxy 3-methoxy-4-n-octyloxybenzalnitrile was reacted with guanidine, using the procedure of Example 9, to give 2,4 - diamino-5 - (3 - methoxy - 4 - n - octyloxybenzyl)-pyrimidine, m.p. 156°.

EXAMPLE 8

2.3 g. Sodium dissolved in 150 ml. alcohol, and 21.3 g. benzaldehyde and 20 g. β-ethoxypropiononitrile were added. The mixture was refluxed for 3 hours and then about 120 ml. alcohol was distilled off. The residue was treated with 150 ml. water and extracted 3 times with ether (300 ml. in all). The extract was dried over sodium sulphate and the ether distilled off. Distillation at 5 mm. and 160—180° gave 10 g. β-ethoxy benzalnitrile (26% yield).

10 g. β-Ethoxy benzalnitrile was refluxed with 60 ml. of an 18.4% w/v solution of guanidine in methanol. After 48 hours the mixture was concentrated to half its original volume and refluxed for a further 48 hours. The solid was filtered off after cooling, washed with aqueous acetone and dried to give 3 g. of 2,4 - diamino - 5 - benzylpyrimidine, melting point 196° (28% yield).

EXAMPLE 9

The use of 3-methoxy-4-n-butoxybenzaldehyde in the procedure described in Example 8 gave a 67% yield of undistilled β-ethoxy 3-methoxy-4-n-butoxybenzalnitrile.

35 g. Crude β-ethoxy 3-methoxy-4-n-butoxybenzalnitrile was mixed with 150 ml. 14.75% w/v guanidine solution in methanol and the mixture refluxed for 24 hours. The solid formed was filtered off, and washed with a little methanol. The mother liquor and washings were concentrated to about 75 ml. and refluxed overnight to give a second crop of solid. The combined solid was washed with aqueous acetone and dried to give 7.6 g. 2,4-diamino - 5 - (3 - methoxy - 4 - n - butoxybenzyl)pyrimidine (21% yield), m.p. 135°.

EXAMPLE 10

A mixture of 14 g. sodium methoxide, 82.5 g. veratraldehyde, 49.5 g. β-ethoxypropiononitrile and 350 ml. dioxan was heated at 100° for 4 hours with occasional shaking. The solvent was distilled off at 25 mm. and the residue was treated with 350 ml. water and extracted with 3 × 133 ml. ether. The ether

solution was dried over sodium sulphate and the ether distilled off. The residue was distilled at 0.9 mm. to give at 172—186° 20 g. β-ethoxy veratralnitrile (16% yield), satisfactory in subsequent condensation with guanidine.

EXAMPLE 11

59 g. Veratraldehyde was dissolved in 200 ml. dry benzene and 35.5 g. β-ethoxypropiononitrile added. The mixture was stirred well and 14 g. ~~sodamine~~ sodamide added. The mixture was stirred under reflux for 5 hours. After cooling the product was treated with 25 ml. alcohol and, cautiously at first, with water to a total of 300 ml. The benzene layer was separated, the water layer was washed with benzene, and the combined benzene layers were dried azeotropically followed by distillation off of the benzene. The product was distilled at 2 mm. and the 21 g. fraction obtained at 150—200° consisted substantially of β-ethoxy veratralnitrile (27% yield), satisfactory in subsequent condensation with guanidine.

EXAMPLE 12

5.8 g. Sodium and a crystal of ferric sulphate were added with stirring to 500 ml. liquid ammonia in a flask supported in an alcohol-solid carbon dioxide cooling bath. When the sodium had dissolved, a mixture of 41.5 g. veratraldehyde and 25 g. β-ethoxypropiononitrile was added. The mixture was stirred for 4 hours and the ammonia evaporated off. The residue was treated with 25 ml. alcohol and, cautiously at first, with water to a total of 250 ml. The mixture was extracted with 3 × 100 ml. ether and the extract dried over sodium sulphate. The ether was distilled off and the residue distilled at 0.5 mm. to give at 160—180° 18 g. β-ethoxy veratralnitrile (29% yield), satisfactory in subsequent condensation with guanidine.

EXAMPLE 13

5.1 g. Sodium was dissolved in 250 ml. alcohol, followed by 24.8 g. veratraldehyde and 20 g. β-bromopropiononitrile. Sodium bromide began to separate out immediately, and after 30 minutes with occasional shaking the mixture was filtered. The filtrate was refluxed for 2 hours and then 200 ml. alcohol was distilled off. The residue was treated with 200 ml. water and extracted with 3 × 67 ml. ether. The extract was dried over sodium sulphate and the ether distilled off. The product was distilled at 1 mm. and the fraction boiling at 170—180° collected to give 18 g. β-ethoxy veratralnitrile (49% yield), satisfactory in subsequent condensation with guanidine.

EXAMPLE 14

6.0 g. Sodium was dissolved in 350 ml. alcohol, followed by 82.5 g. veratraldehyde and 49 g. β-dimethylaminopropiononitrile. The mixture was refluxed for 6 hours with slow distillation of solvent; the original volume was restored by addition of dry alcohol every half-hour. 300 ml. Alcohol was then distilled off and the residue was treated with 300 ml. water and extracted with 3 × 100 ml. ether. The extract was dried over sodium sulphate and the ether distilled off. The product was distilled at 0.7 mm. to give at 150—175° 35 g. of a mixture of β-dimethylamino and β-ethoxy ~~veratralnitrile~~ veratralnitriles (32% yield), which was satisfactory in subsequent cyclisation with guanidine to give 2,4 - diamino - 5 - (3,4-dimethoxybenzyl)pyrimidine.

EXAMPLE 15

1.2 g. Sodium was dissolved in 100 ml. alcohol, followed by 13 g. veratraldehyde and 10.2 g. β - n - propylthiopropiononitrile. The mixture was refluxed for 4 hours with slow distillation of solvent; the volume was restored with fresh alcohol at half-hourly intervals. A smell of mercaptan in the distillate indicated that as expected some β-propylthio groups were being replaced with β-ethoxy groups derived from the solvent. Most of the alcohol was then distilled off. The residue was treated with 100 ml. water and extracted with 2 × 50 ml. ether. The extract was dried over sodium sulphate and the ether distilled off, finishing under water-pump vacuum. The residual veratralnitrile weighed 15 g. (73% yield) and was satisfactory in subsequent cyclisation with guanidine to give 2,4 - diamino - 5 - (3,4-dimethoxybenzyl)pyrimidine.

EXAMPLE 16

10.5 g. Acrylonitrile was added slowly with stirring to 200 ml. of solution obtained from a mixture of 1.5 g. sodium in 100 ml. methanol and 3.5 g. magnesium in 150 ml. methanol. 33.2 g. Veratraldehyde was added after 15 minutes, and the solution was refluxed. After 5 minutes the solution had become turbid and the amount of precipitated magnesium hydroxide thereafter increased markedly. A solution of 1 g. sodium in 85 ml. methanol was added to the remaining sludge of sodium-magnesium methoxide and filtered rapidly, and the filtrate was added to the reaction mixture. The mixture was reduced to 150 ml. by boiling, refluxed for 7 hours, and allowed to stand overnight. Ice, 150 ml. 2 N-hydrochloric acid and 100 ml. ether were stirred in. An oil separated and solidified. This solid was filtered off and dissolved in an ether-benzene mixture. The solution was washed successively with water, potassium bisulphite solution (until the washings were free from aldehyde), water, dilute aqueous sodium hydroxide, and water. The solution was dried over anhydrous potassium carbonate, evaporated to small volume, and diluted with hexane.

A cream-coloured solid separated and was washed with ether to give 10 g. β-methoxy veratralnitrile, m.p. 71—73°. The mother liquor weighed 16.5 g. and yielded a second crop of 7 g. solid melting at 69—78°. The filtrate from the original solidified oil was extracted with ether and treated by the procedure described above, to give 9 g. of less pure veratralnitrile. The mother liquors from the crystallisation of the solid fractions were combined and evaporated leaving 14 g. residue. This gave 12 g. distillate at 0.1 mm. and 125—130°. A refrigerated methanolic solution of the distillate deposited 3 g. crystalline veratralnitrile. The total weight of crystalline veratralnitrile was 29 g. (62% yield); 11% of the initial veratraldehyde was recovered from the bisulphite extractions, and the distilled but uncrystallisable oil accounted for about 20%. The crystalline veratralnitrile after recrystallisation from methanol melted at 73° and analysed correctly for $C_{13}H_{15}NO_3$. It had maximum ultraviolet absorption at 321 mμ (e=14700), 295 mμ (e=12250) and 238 mμ (e=11300) indicating the structure α-veratrylidene-β-methoxypropiononitrile.

Unlike the crystalline veratralnitrile, the uncrystallisable oil had maximum ultraviolet absorption at 290—320 mμ (plateau, e=about 6000), 287 mμ (e=6300) and 230 mμ (e=9300). Analysis of this absorption indicates that about 25% of the oil could be the veratralnitrile of m.p. 73° and that at least two other substances are present. A solution of 2 g. of the oil in 15 g. methanol containing a little sodium methoxide was refluxed for 6 hours and refrigerated overnight, giving 0.5 g. of crystals, m.p. 71—73°. The oil is therefore believed to be a mixture of position and geometrical isomers of the veratralnitrile of m.p. 73°.

20 mM. (4.7 g.) α-Veratrylidene-β-methoxypropiononitrile was dissolved in 30 ml. methanol containing in solution 60.6 mM guanidine (as shown by titration). The solution was heated at 56° for 24 hours, while nitrogen gas was passed through the reaction mixture. The volume of the reaction mixture after heating was about 25 ml. It was filtered hot, and the solid was washed with 25 ml. hot methanol to give 2.4 g. fairly pure 2,4-diamino - 5 - (3,4 - dimethoxybenzyl)-pyrimidine (44% yield). Similar experiments using 2.0, 1.5 and 1.0 equivalents of guanidine gave yields of 40%, 37% and 25% respectively.

No difficulties have been observed in preparations on a much larger scale.

Example 17

12 g. Acrylonitrile and 30 g. piperonal were reacted by the procedure of Example 16 with a reflux period of 20 hours. The β-methoxy piperonalnitrile was worked up as described in Example 16 for the veratralnitrile but did not crystallise as readily. Therefore the solvent was evaporated and the residual oil was distilled at 1 mm. giving at 135—180° 35 g. of a colourless oil. This was dissolved in 50 ml. methanol and refrigerated overnight, depositing a solid which after washing with cold methanol weighted 17.5 g. and melted at 47—48°. After one recrystallisation from methanol it melted at 50—51°, analysed correctly for $C_{12}H_{11}O_3N$, and had maximum ultraviolet absorption at 326 mμ (e=13500), 292 mμ (e=9500) and 237 mμ (e=11200), indicating the structure α-piperonylidene-β-methoxypropiononitrile.

20 mM (4.4 g.) α-Piperonylidene-β-methoxypropiononitrile was added to 40 ml. methanol containing 60 mM dissolved guanidine. The reaction mixture was warmed to 50° while 20 ml. methanol was removed *in vacuo*. The mixture was heated at 50° for 26 hours. The contents were filtered hot and washed with hot methanol to give 2.8 g. of a yellow solid, m.p. 231° after darkening. It was dissolved in 50 ml. 5% acetic acid and the solution brought to pH 5 with added dilute aqueous sodium hydroxide. Much yellow material precipitated and was removed. The filtrate was treated with charcoal, filtered, and brought to pH 10. A cream-coloured solid separated. This process was repeated to give 1.8 g. 2,4-diamino - 5 - (3,4 - methylenedioxybenzyl)-pyrimidine, m.p. 238° still not pure. This solid was slurried with 5% aqueous potassium hydroxide, filtered, washed free of alkali and recrystallised from 80% ethanol. Well-formed, very pale yellow prisms separated having the correct composition for the desired pyrimidine.

Example 18

14.5 g. Acrylonitrile was warmed in a solution obtained from 2.5 g. sodium in 100 ml. methanol. After 15 minutes, 31 g. 1-naphthaldehyde and a solution of 5 g. magnesium dissolved in 150 ml. methanol were added. The reaction mixture was refluxed for 23 hours, cooled, diluted with water and ice, and acidified with hydrochloric acid. The mixture was partitioned between ether and water; and the ethereal layers were washed with sodium bisulphite solution (to remove any 1-naphthaldehyde), water, sodium carbonate solution, and again with water. The ethereal layer was dried finally over potassium carbonate. After evaporation of the solvent, the oil was dissolved in ether-hexane and chromatographed on alumina. Some colour was removed, but no solid could be obtained from the eluate fractions. These fractions were finally combined and distilled in high vacuum. The β-methoxy 1-naphthalnitrile was obtained in 75% yield as a yellow oil, probably a mixture of isomers, boiling at 95—100° at 1 μ and having an absorption maximum at 280 mμ.

12 g. β-Methoxy 1-naphthalnitrile was added to 100 ml. guanidine solution, prepared by mixing a solution of 3.5 g. sodium in 50 ml. methanol with a solution of 15 g. guanidine hydrochloride in 25 ml. methanol and filtering off the precipitated sodium chloride. The mixture was heated to boiling with stirring, boiled until the volume had diminished to 75 ml., and then refluxed for 23 hours. The colour, initially a pale yellow, did not increase during this time. A precipitate appeared 3.5 hours after boiling began, and reaction may well have been substantially complete shortly thereafter. The reaction mixture was filtered hot, and the precipitate was washed with methanol. This crop of the product weighed 9.8 g. and 0.4 g. more was obtained from the mother liquors on cooling (80% yield). This material melted at 240—241° after recrystallisation from 80% alcohol. Its composition was correct for 2,4 - diamino - 5 - (1 - naphthylmethyl)-pyrimidine. At pH 1 it had absorption maxima at 273 mμ (e=11500) and 281 mμ (e=11750) and a minimum at 252 mμ (e=6900), and at pH 11 it had an absorption maximum at 284 mμ (e=13150) and a minimum at 253 mμ (e=5000). It formed a hydrochloride very sparingly soluble in water.

EXAMPLE 19

8 g. Sodium methoxide was added to 120 ml. benzene, followed by 16.5 g. veratraldehyde and 10 g. β-ethoxypropiononitrile, and the mixture was warmed at 30°. After 15—20 minutes, the slurry had set to a gel, which was broken up; heating was resumed at 45—50° with formation of a gel again. This was broken up and the mixture stood overnight at room temperature. To half of this slurry was added the filtrate from 4.8 g. guanidine hydrochloride and 2.7 g. sodium methoxide in 80 ml. ethanol. The mixture was heated and the benzene ethanol azeotrope boiled off at 68° with liquid level kept up by ethanol addition. The slurry was refluxed for 7—8 hours, cooled and filtered. The cake was resuspended in a little water, when crystals formed. The crystals were filtered off, washed with a little water and dissolved in a small amount of water plus a few drops of acetic acid. The solution was brought to pH 8—9 with ammonia water, and crystals formed again giving 1.0 g. of yellow material, m.p. 223—229° with maximum ultraviolet absorption at 275 mμ at pH 1 and at 285 mμ at pH 11, identical with authentic 2,4-diamino-5-(3,4-dimethoxybenzyl)pyrimidine.

EXAMPLE 20

3 g. Sodium was dissolved in 150 ml. methanol, followed by 41.1 g. veratraldehyde and 25 g. β-ethoxypropiononitrile, and the mixture was refluxed for 3 hours on the steam bath. Then 94 ml. of a 47% w/v solution of guanidine in methanol was added and the refluxing continued for 24 hours with stirring. The mixture was cooled and 22 g. yellow solid was filtered off. The mother liquors were concentrated to half volume and refluxed again for 24 hours and a further 5 g. solid was obtained. The combined crop was dissolved in dilute acetic acid, treated well with charcoal, and filtered. The filtrate was brought up to pH 9 by the addition of ammonia solution and left to stand for 2 hours. The white product was filtered off, washed with water and acetone and dried to give 20 g. 2,4-diamino - 5 - (3,4 - dimethoxybenzyl)-pyrimidine, m.p. 228° (31% yield, reckoned on veratraldehyde).

Using the same reagents, quantities and procedure, but adding the guanidine solution before commencing reflux, 2,4-diamino-5-(3,4-dimethoxybenzyl)pyrimidine was obtained more slowly, but the yield was at least 11 g. (17%).

EXAMPLE 21

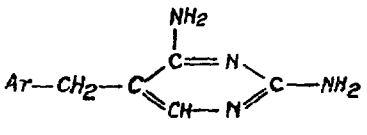
1.0 kg. Sodium methoxide and 5.8 kg. veratraldehyde were dissolved in 20 litres methanol and 3.5 kg. β-ethoxypropiononitrile was added. The mixture was refluxed overnight with stirring in a steam-heated stainless-steel vessel. A solution containing 5.2 kg. guanidine in 35 litres methanol was added and the mixture refluxed for 36 hours with stirring. The solid that separated was filtered off, washed with methanol and dried to give 3.5 kg. crude product. The mother liquors after concentration yielded a further 0.3 kg. After purification, 2.25 kg. 2,4-diamino-5-(3,4-dimethoxybenzyl)pyrimidine (25% yield), m.p. 227°, was obtained.

EXAMPLE 22

12 g. Sodium was dissolved in 600 ml. ethanol, followed by 180 g. 3-methoxy-4-ethoxybenzaldehyde and 99 g. β-ethoxypropiononitrile, and the mixture was refluxed for 2.5 hours. Then 1200 ml. of a 14.4% w/v solution of guanidine in methanol was added, and refluxing continued for 6 hours. The solid that separated was filtered off, washed with methanol and dried to give 80 g. 2,4 - diamino - 5 - (3 - methoxy - 4-ethoxybenzyl)pyrimidine (29% yield), m.p. 185°. The recrystallised material had m.p. 188—190°.

WHAT WE CLAIM IS:—

1. A method for making a 2,4-diamino-5-arylmethylpyrimidine of formula II,



(II)

* C L M S *

12 g. β-Methoxy 1-naphthalnitrile was added to 100 ml. guanidine solution, prepared by mixing a solution of 3.5 g. sodium in 50 ml. methanol with a solution of 15 g. guanidine hydrochloride in 25 ml. methanol and filtering off the precipitated sodium chloride. The mixture was heated to boiling with stirring, boiled until the volume had diminished to 75 ml., and then refluxed for 23 hours. The colour, initially a pale yellow, did not increase during this time. A precipitate appeared 3.5 hours after boiling began, and reaction may well have been substantially complete shortly thereafter. The reaction mixture was filtered hot, and the precipitate was washed with methanol. This crop of the product weighed 9.8 g. and 0.4 g. more was obtained from the mother liquors on cooling (80% yield). This material melted at 240—241° after recrystallisation from 80% alcohol. Its composition was correct for 2,4 - diamino - 5 - (1 - naphthylmethyl)-pyrimidine. At pH 1 it had absorption maxima at 273 mμ (e = 11500) and 281 mμ (e = 11750) and a minimum at 252 mμ (e = 6900), and at pH 11 it had an absorption maximum at 284 mμ (e = 13150) and a minimum at 253 mμ (e = 5000). It formed a hydrochloride very sparingly soluble in water.

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Using the same reagents, quantities and procedure, but adding the guanidine solution before commencing reflux, 2,4-diamino-5-(3,4-dimethoxybenzyl)pyrimidine was obtained more slowly, but the yield was at least 11 g. (17%).

EXAMPLE 21

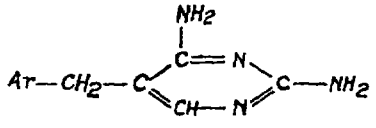
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12 g. Sodium was dissolved in 600 ml. ethanol, followed by 180 g. 3-methoxy-4-ethoxybenzaldehyde and 99 g. β-ethoxypropiononitrile, and the mixture was refluxed for 2.5 hours. Then 1200 ml. of a 14.4% w/v solution of guanidine in methanol was added, and refluxing continued for 6 hours. The solid that separated was filtered off, washed with methanol and dried to give 80 g. 2,4 - diamino - 5 - (3 - methoxy - 4-ethoxybenzyl)pyrimidine (29% yield), m.p. 185°. The recrystallised material had m.p. 188—190°.

WHAT WE CLAIM IS:—

1. A method for making a 2,4-diamino-5-arylmethylpyrimidine of formula II,



(II)

wherein Ar is a phenyl group optionally substituted with alkoxy, alkyl, amino, dialkylamino, and/or halogen or with .CH:CH.CH:CH., characterised in that a corresponding aromatic aldehyde Ar.CHO is condensed in the presence of a strong base with a β-substituted propionitrile of formula $Y.CH_2.CH_2.CN$, wherein Y is an electrophilic group, to give as an intermediate product a substance consisting of one or more nitriles of formulae Ia and Ib,

$$Ar.CH:C(CN).CH_2.Z \quad \text{(Ia)}$$

$$Ar.CH_2.C(CN):CH.Z \quad \text{(Ib)}$$

wherein Ar is the aromatic residue of the aldehyde starting material and Z is the electrophilic group Y of the β-substituted propiononitrile or an alkoxy group derived from a solvent alcohol, and the intermediate product is condensed with guanidine to form the desired pyrimidine II.

2. A method claimed in Claim 1, characterised in that a β-alkoxypropiononitrile is used.

3. A method claimed in Claim 1 or Claim 2, characterised in that the aromatic aldehyde is condensed with the β-substituted propiononitrile in the presence of alkoxide anion in an alcoholic solvent.

4. A method claimed in Claim 3, characterised in that a β-alkoxypropiononitrile is formed *in situ* from acrylonitrile and the solvent alcohol.

5. A method claimed in any of Claims 1 to 4, characterised in that the intermediate product is condensed with guanidine in an alcoholic solvent using from two to three equivalents of guanidine.

6. A method claimed in any of Claims 1 to 5, characterised in that the aromatic aldehyde used is a 3,4-dialkoxybenzaldehyde with or without further substituents in the ring.

7. A method claimed in Claim 6 characterised in that veratraldehyde is used to produce 2,4 - diamino - 5 - (3,4 - dimethoxybenzyl)pyrimidine.

8. A method claimed in Claim 6, characterised in that 3,4,5-trimethoxybenzaldehyde is used to produce 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine.

9. A method claimed in any of Claims 1 to 8 characterised in that the process is conducted in one operation without isolation of an intermediate product.

10. A method claimed in Claim 3, or any of Claims 4 to 9 as dependent on Claim 3, for making 2,4 - diamino - 5 - arylmethylpyrimidines of formula II in which Ar is a phenyl group having an alkoxy substituent (RO) in the 2 or 4 position, characterised in that the corresponding alcohol (ROH) is used as solvent.

11. A method claimed in Claim 1, substantially as herein described with reference to any of Examples 1, 2 (paragraphs 1, 2 and 3) 3, 4 and 8 to 17.

12. A method claimed in Claim 1, substantially as herein described with reference to Example 19 or Example 20.

13. A method claimed in Claim 1, substantially as herein described with reference to any of Examples 5, 6, 7, 18, 21 and 22.

14. A 2,4-diamino-5-arylmethylpyrimidine made by the method claimed in any of Claims 1 to 8 and 11, or its obvious chemical equivalent.

15. A 2,4-diamino-5-arylmethylpyrimidine made by the method claimed in Claim 9 or Claim 12, or its obvious chemical equivalent.

16. A 2,4-diamino-5-arylmethylpyrimidine made by the method claimed in Claim 10 or Claim 13, or its obvious chemical equivalent.

17. A method for making a substance consisting of one or more nitriles of formulae Ia and Ib

$$Ar.CH:C(CN).CH_2.Z \quad \text{(Ia)}$$

$$Ar.CH_2.C(CN):CH.Z \quad \text{(Ib)}$$

wherein Ar is a phenyl group optionally substituted with alkoxy, alkyl, amino, dialkylamino, and/or halogen or with .CH:CH.CH:CH., and Z is an electrophilic group, characterised in that a corresponding aromatic aldehyde Ar.CHO is condensed in the presence of a strong base with a β-substituted propiononitrile of formula $Y.CH_2.CH_2.CN$ wherein Y is an electrophilic ether, thioether or tertiary amino group, the electrophilic group Z being the electrophilic group Y of the β-substituted propiononitrile or an alkoxy group derived from a solvent alcohol.

18. A method claimed in Claim 17, characterised in that a β-alkoxypropiononitrile is used.

19. A method claimed in Claim 17 or Claim 18, characterised in that the aromatic aldehyde is condensed with the β-substituted propiononitrile in the presence of alkoxide anion in an alcoholic solvent.

20. A method claimed in Claim 19, characterised in that a β-substituted propiononitrile is formed *in situ* from acrylonitrile and the solvent alcohol.

21. A method claimed in any of Claims 17 to 20, characterised in that the aromatic aldehyde used is a 3,4-dialkoxybenzaldehyde with or without further substituents in the ring.

22. A method claimed in Claim 21, characterised in that the aromatic aldehyde used is veratraldehyde.

23. A method claimed in Claim 21, characterised in that the aromatic aldehyde used is 3,4,5-trimethoxybenzaldehyde.

24. A method claimed in Claim 17, substantially as herein described with reference to any of Examples 1, 2 (paragraphs 1, 2 and 3), 3, 4 and 8 to 17.

25. A method claimed in Claim 17, substantially as herein described with reference to any of Examples 5, 6, 7 and 18.

26. A product made by the method claimed in any of Claims 17 to 24 or its obvious chemical equivalent.

27. A product made by the method claimed in Claim 25 or its obvious chemical equivalent.

28. A β-substituted α-arylmethylidene-propiononitrile of formula Ia,

$$Ar.CH:C(CN).CH_2.Z \quad (Ia)$$

wherein Ar has from 6 to 15 carbon atoms and is a phenyl group optionally substituted with alkoxy and/or halogen or with .CH:CH.CH:CH., and Z is an alkoxy group.

29. A product claimed in Claim 28 which is a β-alkoxy α-3,4-dialkoxybenzylidene-propiononitrile with or without further substituents in the ring.

30. α-Veratrylidene-β-methoxypropiono-nitrile.

31. α-Veratrylidene-β-ethoxypropiono-nitrile.

32. α-3,4,5-Trimethoxybenzylidene-β-methoxypropiononitrile.

33. α-3,4,5-Trimethoxybenzylidene-β-ethoxypropiononitrile.

34. α-Piperonylidene-β-methoxypropiono-nitrile.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1964. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

