COMMISSIONER'S DECISION SUMMARY

C.D. 1218 ....Application No. 461,212 (F01, O)

Certain claims rejected as disclosing a known compound.

The application disclosed certain compounds having anti-viral activity and the examiner rejected certain claims on the grounds that a prior art reference disclosed one of the compounds claimed along with the process of its manufacture. The Board recommended that the rejection be reversed since the reference cited, in the opinion of the Board, did not justify a finding of either anticipation or obviousness in the case.

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 461,212, having been rejected under Subsection 47(2) of the Patent Rules, the Applicant asked that the Final Action of the Examiner be reviewed. The rejection has been considered by the Patent Appeal Board and by the Commissioner of Patents. The findings of the Board and the decision of the Commissioner are as follows:

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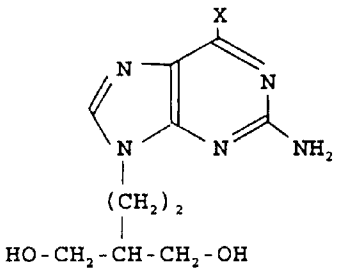
This decision deals with a request that the Commissioner of Patents review the Examiner's Final Action on patent application number 461,212 (Class 260-242.3) which was filed on August 16, 1984. The Applicant is Beecham Group p.l.c., assignee of inventors Richard Lewis Jarvest and Michael Raymond Harnden and the invention is entitled "PHARMACEUTICAL COMPOSITION". The Examiner in charge issued a Final Action on November 7, 1989 rejecting certain claims of the application in view of a literature reference and the Applicant replied on May 7, 1990 requesting that the rejection of the claims be reviewed by the Commissioner of Patents and that a hearing before the Patent Appeal Board be convened for that purpose. Consequently a hearing was held on November 6, 1996 with M. Howarth and J. Hilchie as the Board members, L. Brooke-Keneford, D. Jarvest and P. Tocher representing the Applicant and B. Booth and S. Arpin representing the Patent Examination Branch. On October 24, 1996, i.e. immediately prior to the hearing, the Applicant filed a further submission in support of its appeal.

The invention is directed to compounds having anti-viral activity, processes for their preparation and pharmaceutical compositions containing them. According to the invention compounds of the formula (I)



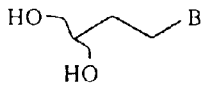
(I)

or a salt, phosphate ester or acyl derivative thereof, in which X represents chlorine, straight or branched chain C_{1-6} alkoxy, preferably methoxy, phenoxy, phenyl C_{1-6} alkoxy, $-NH_2$, -OH or -SH with the proviso that, when X is -OH, the compound of formula (I) is in a purity state of greater than 50% by weight of pure compound are provided.

In his Final Action the Examiner rejected claims 1, 4 to 7, 10, 15, 18 to 20, 22 to 27 and 30 stating that:

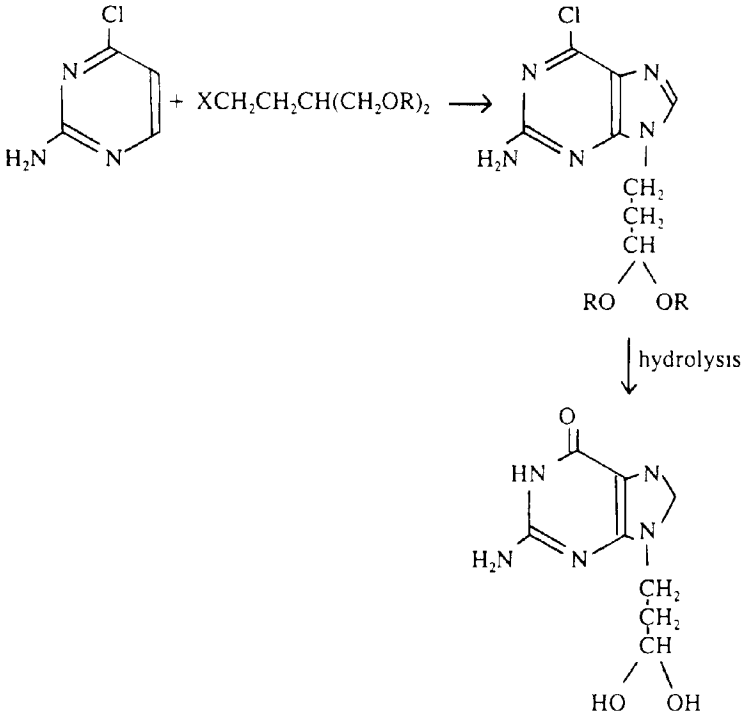
> Applicant's letter of May 30, 1988 has been received and the application has been reviewed having regard to applicant's arguments However, it has been decided that these arguments do not overcome the objections set forth in the last Official Action
>
> The number of claims in this application is 32
>
> Reference Re-Applied.
>
> Synthetic Communications 2(b) Pages 345-351 1972 Eggelte et al

Eggelte et al on pages 345 and 346 discloses that molecular systems having the following structure have pharmaceutical activity as anti-viral agents



wherein B is a nucleobase

As an example of a nucleobase, Eggelte et al prepared the corresponding guanine derivative as follows



wherein R is benzyl

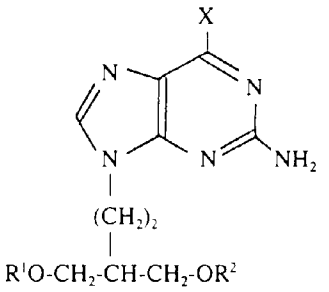
Therefore the process of making the benzyl derivative and its corresponding hydrolyzed derivative, as well as the compounds per se, are old as illustrated by Eggelte et al A better method of making the compounds does not bestow patentability onto the old products Therefore claims 1, 4 to 7, 10, 15, 18 to 20 and 22 to 27 are rejected as being too broad as to include subject matter taught in Eggelte et al

In addition, since Eggelte et al were making anti-viral agents, it would be obvious to one skilled in the art to prepare the corresponding pharmaceutical composition having anti-viral activity with an effective amount of the desired compound Hence, claim 30 is rejected for lack of inventive ingenuity

Applicant's argument that " the claims covering this compound in pure form are neither anticipated nor obvious over the prior art, since without the discovery of anti-viral activity in the compound, not only was it never produced in a pure form but there would have been no reason to do so " is rejected First, as stated previously, Eggelte did want to prepare these compounds as anti-viral agents (page 346) Second, Eggelte did prepare the compound per se, albeit not in 100% yield (ie pure) Hence the compound and its process of making it is anticipated by Eggelte Moreover, it would be obvious as stated above to prepare the pharmaceutical composition once the compound has been prepared

Claims 1, 20 and 24 which are representative of the rejected claims are as follows:

1 A process for the preparation of a compound of formula (II)



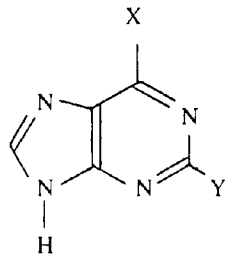
(II)

or pharmaceutically acceptable salts thereof in which X represents chlorine, straight or branched chain C_{1-6} alkoxy, phenoxy, phenyl C_{1-6} alkoxy, $-NH_2$, -OH or -SH, with the proviso that, when X is -OH, the compound of formula (I) is isolated in a purity state of greater than 50% by weight of pure compound with respect to the mono- and di-benzyl ethers thereof

and each of R^1, R^2 and R^3 represents hydrogen or an acyl group of formula R^4-CO- in which R^4 is C_{1-18} alkyl or imidazolyl, or R^1 or R^2 represents a phosphate ester group of formula $(HO)_2$-PO-, or R^1 and R^2 together represent a O P bridging group, HO

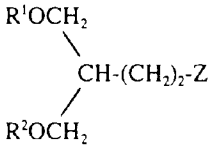
said process comprising the steps of

A treating a compound of formula (IV)



(IV)

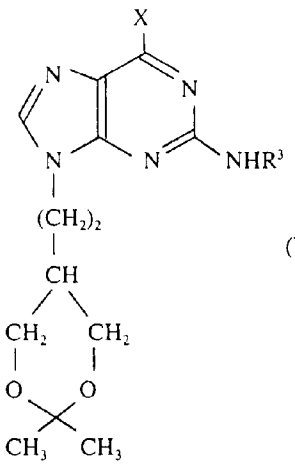
wherein Y is chlorine or $-NHR^3$, and X and R^3 are as defined above, with a compound of formula (Va)



(Va)

wherein R^1 and R^2 are as defined above and Z is a leaving group and, where Y is chlorine, converting it to an $-NHR^3$ group, or

B hydrolysing the 1,3-dioxane ring of a compound of formula (VIIa)

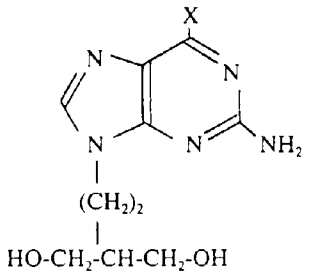


(VIIa)

wherein X and R^3 are as defined above, provided that R^3 is not acyl when X is other than OH,

and, where required, converting the product of either of process steps A and B to a pharmaceutically acceptable salt, phosphate ester or acyl derivative thereof

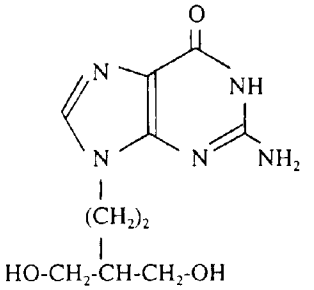
20 A compound of formula (I)



(I)

or a salt, phosphate ester or acyl derivative thereof, in which X represents chlorine, straight or branched chain C_{1-6} alkoxy, phenoxy, phenyl C_{1-6} alkoxy, $-NH_2$, -OH or -SH, said acyl derivative being one wherein one or both of the hydrogens in the acyclic -OH groups, and/or one of the hydrogen atoms in the $-NH_2$ group, are replaced by R-CO- groups, wherein R is hydrogen, C_{1-18} alkyl, phenyl, phenyl C_{1-6} alkyl or imidazolyl, with the proviso that, when X is -OH, the compound of formula (I) is in a purity state of greater than 50% by weight of pure compound with respect to the mono- and di-benzyl ethers thereof

24 A compound according to claim 1, of formula (A)



(A)

in a purity state of greater than 60% by weight of pure compound, or a pharmaceutically acceptable salt thereof

In its response to the Final Action the Applicant submitted a new set of claims numbered 1 to 46 to replace claims 1 to 32, the main differences, apart from numbering changes, between the two sets of claims being the addition of new process claims 8 to 10 and the addition of use claims 37 to 46 and it is these new claims which will be considered by the Board.

The basis of the Examiner's rejection of the claims is the Eggelte reference so that the issues before the Board are whether or not Eggelte (a) discloses either a process or compound covered by any of the rejected claims so as to render those claims either obvious or anticipated or (b) discloses the utility of the compounds claimed in the application.

In assessing the Eggelte reference the Board notes that the Applicant listed the reference as prior art on page 1 of the disclosure stating that:

> The compound 9-(4-hydroxy-3-hydroxymethylbut-1-yl) guanine of formula (A)
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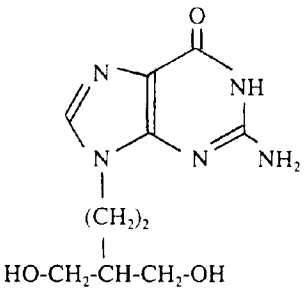
> 
> (A)
>
> is disclosed in Synthetic Communications, 2(6), 345-351 (1972) but no pharmaceutical activity has been indicated for the compound in this or any other published document We have repeated the synthesis of the compound as described in the above publication, and have shown that the product is a mixture of the compound of formula (A), its monobenzyl ether and its dibenzyl ether, this mixture having a melting point and uv spectrum in agreement with those reported in the publication for the supposedly 'pure' compound of formula (A) Our analysis of the product produced by the above synthesis showed that it contained 45-50 % by weight of the compound of formula (A), 45-50% by weight of the monobenzyl ether and 5% or less by weight of the dibenzyl ether

During the prosecution of the application the Applicant has steadfastly maintained this interpretation of the Eggelte reference, providing a substantial number of documents and argument to support its position. Thus in its response to the Final Action the Applicant stated that part of the Eggelte reference was taken from the doctoral thesis of W.F.A. Grose, one of the co-authors of the paper. A translation of the relevant parts of that thesis clearly show that Grose did not prepare pure 9-(4-hydroxymethylbut-11-yl) guanine since it was stated that it was not possible to obtain a microanalysis result that fitted.

Also included with the response was an affidavit from Dr. Jarvest stating that he had repeated the reported synthetic sequence used in Eggelte to allegedly prepare the compound of formula (A) but obtained only a mixture of the desired compound with its mono and dibenzyl ethers, the desired compound comprising less than 50% of the total.

In the submission of October 24, 1996 the Applicant referred to a declaration by Dr. Harnden filed in connection with Applicant's United States patent application number 085,216 confirming the results obtained when Dr. Jarvest repeated the Eggelte synthesis and stating that the structure and characteristics of the Eggelte product were so unclear that Eggelte would not enable one of ordinary skill in the anti-viral art to prepare substantially pure 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine.

In the same response the Applicant also referred to United States patent number 4,845,084 issued on July 4, 1989 where the authors' attempts to repeat the Eggelte procedure were reported to result not in the production of 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine but in the production of 9-(4-chloro-3-hydroxymethylbut-1-yl)guanine.

After reviewing all of this material along with the Applicant's various submissions and in conjunction with the presentation at the hearing the Board is of the opinion that Eggelte does not show the preparation of pure 9-(4-hydroxymethylbut-1-yl) guanine and does not therefore anticipate or render obvious any of the rejected claims.

As to the Examiner's contention that Eggelte was making anti-viral agents the Board considers this to be an overstatement of what is contained in the reference. From the material submitted by the Applicant, notably the translations of parts of the Grose thesis provided both in the response to the Final Action and at the hearing, it is obvious that Eggelte was concerned with chemical synthesis not pharmaceutical activity. There is no evidence in Eggelte that testing for any pharmaceutical activity let alone anti-viral activity was conducted. At best the statements relating to the utility of the compounds disclosed in Eggelte are mere statements that the compounds might have potential as anti-mitotic or anti-viral agents. While these statements might be an indication of where to start if one were looking for novel anti-viral agents they fall far short of statements of actual utility for the compounds disclosed.

Also the four references referred to on page 10 of the submission of October 24, 1996 would tend to lead a researcher away from Eggelte since they indicate that, while 9-substituted guanine acyclonucleosides containing an ether oxygen atom in the second position of the 9-side chain are highly efficacious as anti-viral agents, replacement of this side-chain ether oxygen atom with carbon as is the case with the compounds disclosed in Eggelte substantially decreases or destroys the anti-viral activity of a compound. Accordingly the Board considers that Eggelte does not disclose the utility of the compounds claimed in the application.

The Board therefore recommends that the rejection of claims 1, 4 to 7, 10, 15, 18 to 20, 22 to 27 and 30 be withdrawn, that new claims 1 to 46 be entered into the application and that the application be returned to the Examiner for further prosecution consistent with these recommendations.

M. Howarth
Member

J. Hilchie
Member

I concur with the recommendations of the Board and return the application to the Examiner for further prosecution consistent with the Board's recommendations.

S. Batchelor
Commissioner of Patents

Dated at Hull, Quebec,
this 11 day of March 97