

**THIS OPINION WAS NOT WRITTEN FOR PUBLICATION**

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 10

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte JANAK SINGH, GREGORY S. BISACCHI,  
JOLLIE D. GODFREY, Jr., TOOMAS MITT, RICHARD H. MUELLER,  
ROBERT ZAHLER and THOMAS P. KISSICK

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Appeal No. 95-0865  
Application 08/007,950<sup>1</sup>

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ON BRIEF

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Before: WINTERS and WILLIAM F. SMITH, Administrative Patent Judges, and McKELVEY, Senior Administrative Patent Judge.

McKELVEY, Senior Administrative Patent Judge.

Decision on appeal under 35 U.S.C. § 134

The appeal is from a decision of the Primary Examiner rejecting claims 6-22 and 25 (Paper 6, page 1, item 4 under

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<sup>1</sup> Application for patent filed January 25, 1993. According to applicants, the application on appeal is a continuation-in-part of application 07/912,384, filed July 13, 1992. The real party in interest appears to be Bristol-Myers Squibb Company.

Appeal No. 95-0865  
Application 08/08/007,950

Part II "Summary of Action"), which are all of the claims in the application on appeal. We reverse, but enter new grounds of rejection pursuant to 37 CFR § 1.196(b) as to Claims 6-9, 11-17, 19-22 and 25. We do not enter new grounds of rejection as to Claims 10 and 18.

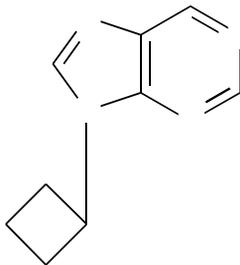
**A. Findings of fact**

The record supports the following findings by a preponderance of the evidence.

The invention

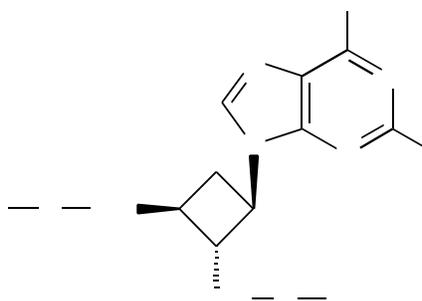
1. The invention relates to a process for making 2-amino-6-halo-9-[2,3-disubstituted-cyclobutyl]-purines.
2. The invention also relates to converting the purines to known antiviral agents, e.g., [1R-(1",2\$,3")] -2-amino-9-[2,3-bis(hydroxymethyl)-cyclobutyl]-1,9-dihydro-6H-purin-6-one.
3. A 9-cyclobutane purine ring has the following structure and

numbering system:

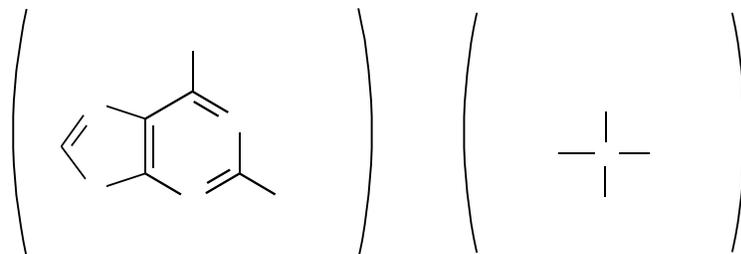


4. Claim 6 reads as follows (paragraph numbering added):

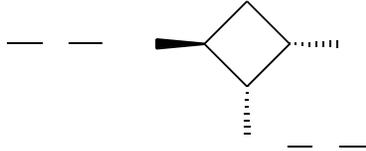
A process for preparing the cyclobutyl purine of the formula



which comprises reacting a purine salt of the formula



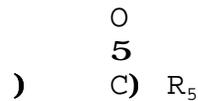
with the bis(2,3-protected hydroxymethyl)cyclobutane of the formula



wherein:

a. Prot is a hydroxy protecting group selected from the group consisting of

- (1) t-butyldimethylsilyl,
- (2) t-butyldiphenylsilyl,
- (3) (tri-phenylmethyl)dimethylsilyl,
- (4) methyldiisopropylsilyl,
- (5) triisopropylsilyl,
- (6) benzyl,
- (7) p-methoxybenzyl, and
- (8) acyl groups of the formula



wherein  $R_5$  is

- (a) straight or branched chain alkyl of 1 to 6 carbon atoms  
or
- (b) phenyl;

b. X is

- (1) a perfluoroalkane sulfonyloxy group,

- (2) a nitro-substituted benzene sulfonyloxy group, or
  - (3) a fluorosulfonyloxy;
- c.  $Y_1$  is chloro, bromo, or iodo;
- d.  $R_1, R_2, R_3$  and  $R_4$  are independently selected from the group consisting of
- (a) straight or branched chain alkyl of 1 to 10 carbons and
  - (b) substituted straight or branched chain alkyl of 1 to 10 carbons;
- (1) [where] substituted straight or branched chain alkyl of 1 to 10 carbons refers to such alkyl groups having one, two, or three substituents selected from the group consisting of
- (a) alkoxy of 1 to 6 carbons and
  - (b) aryl; and
- (2) [where] aryl refers to phenyl and phenyl having one, two, or three substituents selected from the group consisting of
- (a) alkyl of 1 to 6 carbons,
  - (b) alkoxy of 1 to 6 carbons, [and]
  - (c) chloro, bromo, iodo and fluoro.

5. Insofar as we have been able to determine, applicants' specification does not describe any particular advantage of the claimed process vis-à-vis prior art processes described in the specification (e.g., those at page 2, line 1 through page 3, line 14).

Appeal No. 95-0865  
Application 08/08/007,950

The examiner's rejections

6. The examiner made the following four rejections in the final rejection (Paper 6).

7. Claims 6-19 and 22 were finally rejected (Paper 6, page 2) as being unpatentable under 35 U.S.C. § 103 over:

- a. **Bisacchi**, U.S. Patent 5,064,961 (1991) or **slusarchyk**, European Patent Application 0 352 013 (published Jan. 24, 1990)
- b. in view of **Searcey**, IMPROVED SYNTHESSES OF N-SUBSTITUTED NITROIMIDAZOLES, Synthetic Communications, Vol. 19, pages 1309-15 (1989).

8. Claims 6-13 and 25 were finally rejected (Paper 6, page 5) as being unpatentable under 35 U.S.C. § 103 over **Hagberg I**, European Patent Application 0 055 239 (published June 30, 1982). In the Examiner's Answer (Paper 9, page 6), the examiner refers to claims 6-13 and 23-24 and does not mention claim 25. Claims 23-24 were cancelled (Paper 5, page 2). Hence, we will assume that the examiner intended in the Examiner's Answer to maintain a rejection claims 6-13 and 25.

9. Claims 20-21 were finally rejected (Paper 6, page 6) as being unpatentable under 35 U.S.C. § 103 over:

Appeal No. 95-0865  
Application 08/08/007,950

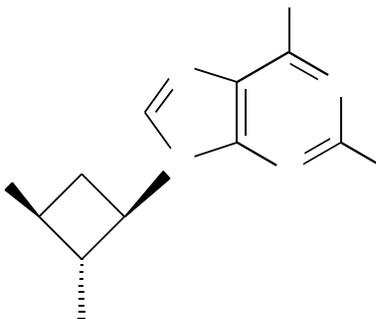
- a. Bisacchi or Slusarchyk
- b. in view of Searcey
- c. further in view of **Hagberg II**, U.S. Patent 4,495,190 (1985).

10. Claims 14-22 were finally rejected (Paper 6, page 6) as being unpatentable under 35 U.S.C. § 103 over:

- a. Hagberg I
- b. in view of Bisacchi, Slusarchyk and Hagberg II.

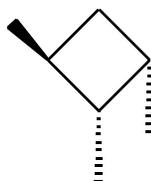
Bisacchi

11. Bisacchi, U.S. Patent 5,064,961 (1991) describes a method for making compounds, including a compound having the formula:

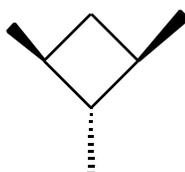


Appeal No. 95-0865  
Application 08/08/007,950

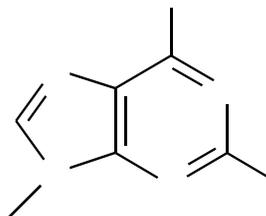
The method involves the reaction of Bisacchi cyclobutane  
Compound 13 (col. 3)



with 2-amino-6-chloropurine (col. 7, last line through col. 8,  
first line) to produce Bisacchi Compound 14 (col. 3)



where W can be 2-amino-6-chloropurine-9-yl (col. 7, lines 32-33):



The reaction takes place in the presence of "a base such as potassium carbonate [K<sub>2</sub>CO<sub>3</sub>], sodium hydride [NaH], and the like, preferably potassium carbonate" (col. 8, lines 5-7).

12. X of Bisacchi Compound 13 is a "leaving group" (col. 3, line 64) such as trifluoromethanesulfonyloxy (triflyl; CF<sub>3</sub>SO<sub>2</sub>O) (col. 3, lines 66-67), corresponding to applicants' claimed X which can be, inter alia, a perfluoroalkane sulfonyloxy group. The Bisacchi X can also be methanesulfonyloxy (mesyl; CH<sub>3</sub>SO<sub>2</sub>O) (col. 3, line 65) or p-nitrobenzenesulfonyloxy (nosyl; O<sub>2</sub>N-C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>O) (col. 4, lines 30-31).

13. The R<sup>4</sup> of Bisacchi's Compounds 13 and 14 is a protecting group such as an acyl group (e.g., acetyl), a benzyl group, t-butyldiphenylsilyl or t-triisopropylsilyl (col. 3, lines 59-63), which corresponds to applicants' "Prot" group when "Prot" is t-butyldiphenylsilyl, t-triisopropylsilyl or an acyl group and applicants' R<sub>5</sub> acetyl, i.e., is alkyl of 1 carbon.

14. Bisacchi lists four possibilities for W (col. 4, lines 31-37 and col. 7, last line through col. 8, first line).

15. The process described by Bisacchi differs from applicants' claim 6 in that Bisacchi describes the use of purines in potassium or sodium salt form whereas applicants claim the use of a purine in its tetraalkylammonium salt form.

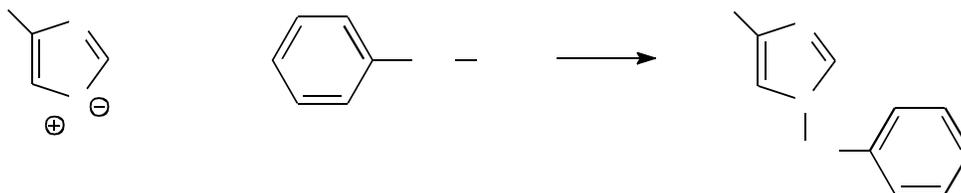
Searcey

16. Searcey describes the reaction of a nitroimidazole with an "appropriate halo compound" (page 1309, first paragraph) to make substituted nitroimidazole compounds. In order to overcome certain yield problems said to occur using then known methods (page 1309, beginning with second full paragraph through page 1310, line 13), Searcey describes an investigation of the reaction of a nitroimidazole compound in the form of a tetraalkylammonium salt with the halo compound (page 1310, lines 13-17).

17. Table 1 (page 1311) of Searcey describes, better yields when the halo compound is reacted with the nitroimidazole compound in the form of a tetraalkylammonium salt vis-à-vis the same nitroimidazole compound in the form of an alkali salt, e.g., a sodium salt.

18. A nitroimidazole in its tetrabutylammonium salt form is described at page 1312.

19. A reaction of nitroimidazole in its tetrabutylammonium salt form with a benzyl halide (e.g., benzyl chloride; first example in Table 1) proceeds generally along the following lines (chemical reaction equation is not balanced):

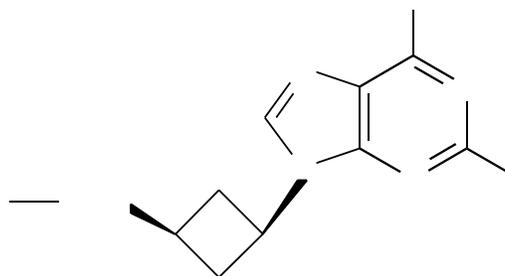


Slusarchyk European Patent Application 0 352 013

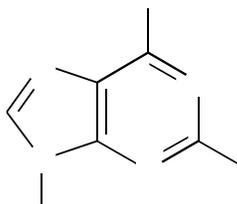
20. Slusarchyk is similar to Bisacchi. As will become apparent, however, there are some differences.

21. Slusarchyk describes the preparation of Compound 15, which is a 2-amino-6-chloro-9-[3-monosubstituted] purine having the formula (page 7, line 47 through page 8, line 10):

Appeal No. 95-0865  
Application 08/08/007,950



22. Slusarchyk Compound 15 is made by reacting  
2-amino-6-chloro-purine (Slusarchyk Compound 14 (page 7)):



with Slusarchyk's cyclobutane Compound 2 (page 5, line 10) having  
the formula:



where:

P is a protecting group, e.g., acyl (page 5, line 20) and  
X is a leaving group, e.g., chloro, bromo, iodo or an aryl  
group (e.g., p-toluenesulfonyloxy) or an alkyl group (e.g.,  
methanesulfonyloxy) (page 5, lines 20-21).

23. The reaction of Slusarchyk Compound 2 with  
Slusarchyk Compound 14 is carried out in the presence of a base,  
such as potassium carbonate, sodium hydride or potassium hydride  
(page 5, line 43).

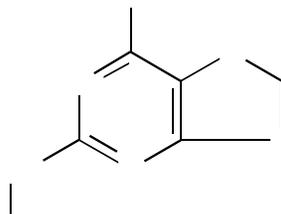
24. Significant disclosure found in Slusarchyk, but  
not found in Bisacchi, is that the leaving group X of Slusarchyk  
Compound 2 is described as including halo groups (chloro, bromo,  
iodo) whereas the corresponding X group of Bisacchi Compound 13  
is not described as including halo groups (col. 3, lines 64  
through col. 4, line 31; col. 7, lines 44-48).

Hagberg I European Patent Application 0 055 239

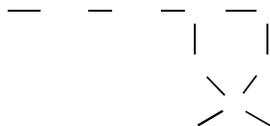
25. Hagberg I describes various organic synthesis  
techniques. One technique of interest is Method of Preparation L  
which begins on the last line of page 15 and continues to line 17  
on page 16.

26. Method L is described as involving a reaction of a  
Compound XII, which is said to have the formula:

Appeal No. 95-0865  
Application 08/08/007,950



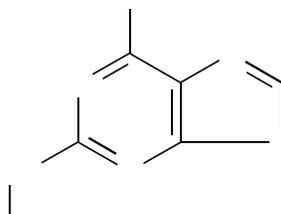
with a Compound XIII (the one on the left side), which has the formula:



27. A person having ordinary skill in the art would immediately recognize that the formula of Compound XII, as set out on page 16 of Hagberg I is erroneous in that a double bond is missing between the 7- and 8-positions in the ring and a hydrogen (H) is missing from the nitrogen (N) at the 9-position. See, e.g., page 56, formula XII which shows the necessary double bond between the 7- and 8-positions and an NH at the 9-position. See

Appeal No. 95-0865  
Application 08/08/007,950

also the formula in Example 10 (page 33). The correct formula would have been understood to be:



28. The reaction of Hagberg I Compound XII with Hagberg I Compound XIII is said to be carried out by "methods known per se" (page 16, line 14).

29. The  $R^7$  of Hagberg I Compound XII may be halo, including chloro, and benzyloxy [page 16, lines 10-11, referring to Method E; page 12, lines 1-3, Y group and referring to Method C1; page 10, line 1,  $X^1$  group and referring to Method B; page 9, lines 19-24 where  $X^1$  is defined inter alia as chlorine (sic-- chloro) and )OR<sup>2</sup> where R<sup>2</sup> can be benzyl].

30. The  $R^{11}$  of Hagberg I Compound XII can be hydrogen [page 16, lines 10-11, referring to Method E; page 12, lines 6-7,

Appeal No. 95-0865  
Application 08/08/007,950

referring R<sup>6</sup> in Method C; and page 10, lines 2-3 where R<sup>6</sup> is defined inter alia as hydrogen].

31. The X<sup>2</sup> of Hagberg I Compound XIII is defined as (page 13, lines 16-19):

a leaving group such as chlorine (sic-chloro), bromine (sic-bromo), iodine (sic-iodo) or a group )SO<sub>2</sub>R<sup>2</sup> where R<sup>2</sup> is defined in Method B \*\*\*.

According to Method B (page 9, lines 21-24):

R<sup>2</sup> is alkyl containing 1-8 carbon atoms, fluorinated alkyl containing 1-8 carbon atoms such as trifluoromethyl, alkylaryl such as benzyl, or aryl such as unsubstituted or substituted phenyl.

32. When X<sup>2</sup> of Hagberg I Compound XIII is )SO<sub>2</sub>R<sup>2</sup> and R<sup>2</sup> is trifluoromethyl, the Compound XIII leaving group is the same as one of the leaving groups described by Bisacchi (X is triflyl) (col. 3, lines 66-67).

33. When X<sup>2</sup> of Hagberg I Compound XIII is )SO<sub>2</sub>R<sup>2</sup> and R<sup>2</sup> is methyl (an alkyl having 1-8 carbon atoms), the Hagberg I Compound XIII leaving group is the same as one of the leaving groups described by Bisacchi (X is mesyl) (col. 3, lines 64-65).

34. R<sup>1</sup> and R<sup>12</sup> of Hagberg I Compound XIII may be alkyl (e.g., methyl) [page 16, lines 9-10, referring to Method A and

page 8, line 36 where R<sup>1</sup> is described as being inter alia alkyl containing 1-8 carbon atoms, with methyl being 1 carbon].

35. Pertinent to the issues involved in this appeal is the method described by Hagberg I in Example 10 (pages 33-34).

Example 10 describes a reaction of

- a. 2-amino-6-benzyloxypurine in the form of a tetrabutylammonium salt [Hagberg I Compound XII where R<sup>7</sup> is benzyloxy ( )OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>) and R<sup>11</sup> is hydrogen ( )H]
- b. with (S)-4-Q-methanesulfonyl-1,2-Q-isopropylidenebutane-1,2,4-triol [Hagberg I Compound XIII (left side) where X<sup>2</sup> is methanesulfonyloxy [i.e., mesyl] and R<sup>1</sup> and R<sup>12</sup> are methyl].

The significant teaching of Example 10 is that a purine in its tetraalkylammonium salt form may be reacted with a compound having a mesyl leaving group. Searcey, on the other hand, describes only the use of halo leaving groups on the compounds reacted with the imidazole in its tetraalkylammonium salt form.

36. Findings with respect to other prior art, e.g., Ichikawa and Zahler, can be found in the Discussion portion of this opinion.

Level of ordinary skill in the art

37. The art involved in this case is the purine art, and more particularly, the reaction of purines with other compounds in such a manner that the other compound attaches to the 9-position of the purine. The prior art (Bisacchi, Slusarchyk, Hagberg I, Ichikawa and Zahler), with the exception of Searcey, is within the field of applicants' endeavor.

38. Searcey, while not dealing with purines, is relevant because it addresses a problem applicants sought and the prior art seeks to solve, viz., attaching moieties to the NH of an imidazole ring, it being noted that a purine includes an imidazole ring.

39. The hypothetical person having ordinary skill in the art would have been aware of the teachings of the prior art mentioned above.

**B. Discussion**

1. The examiner's rejection based on Bisacchi, Slusarchyk and Searcey

The examiner rejected claims 6-19 and 22 under 35 U.S.C. § 103 over Bisacchi, Slusarchyk and Searcey. All of these claims require the use of a protected disubstituted cyclobutane having a leaving group X which is one of:

Appeal No. 95-0865  
Application 08/08/007,950

- (1) a perfluoroalkane sulfonyloxy group,
- (2) a nitro-substituted benzene sulfonyloxy group, or
- (3) a fluorosulfonyloxy.

Bisacchi and Slusarchyk describe reaction of a purine in its alkali salt form and a cyclobutane. Neither describes the use of a purine in its tetraalkylammonium salt form.

Searcey describes the reaction of an imidazole in its tetraalkylammonium salt form with compounds having leaving groups which are halo groups.

The difficulty with the examiner's position is that there is nothing in Searcey which would suggest that the imidazole in its tetraalkylammonium salt form would also react with compounds having leaving groups X called for by the claims. There is no teaching in the combination of Bisacchi, Slusarchyk, and Searcey which would show any interchangeability between the use of purines in their alkali salt forms with purines in their tetraalkylammonium salt forms. Thus, without something more,<sup>2</sup> we regard the examiner's rejection to have been based on impermissible hindsight. Compare In re McLaughlin, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971).

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<sup>2</sup> As will become apparent, infra, we found that "something more" in the teachings of Hagberg I, Ichikawa and Zahler.

Appeal No. 95-0865  
Application 08/08/007,950

The decision of the examiner rejecting claims 6-19 and 22 based on Bisacchi, Slusarchyk and Searcey is reversed.

2. The examiner's rejection based on Hagberg I

The examiner rejected claims 6-13 and 25 as being unpatentable under 35 U.S.C. § 103 over Hagberg I.

With reference to Method of Preparation L and Example 10, Hagberg I differs from the subject matter of claim 6 in that Hagberg I does not describe the reaction of a cyclobutane with a purine.

Thus, it can be said that Hagberg I does not describe at least one of applicants' starting materials, i.e., the cyclobutane. According to the examiner, the failure of Hagberg I to describe the cyclobutane starting materials is of no moment. In support of his position, the examiner cites and relies on In re Durden, 763 F.2d 1406, 226 USPQ 359 (Fed. Cir. 1985). More to the point, in our opinion, is In re Ochiai, 71 F.3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995). The mere fact that a compound with a mesyl group has been reacted with a purine does not per se establish that it would have been obvious to react a cyclobutane with a mesyl group with a purine. Based on Hagberg I alone, we discern no reason, motivation or suggestion to use a cyclobutane

Appeal No. 95-0865  
Application 08/08/007,950

in place of Hagberg I Compound XIII in the Method of Preparation L or Example 10.

The decision of the examiner rejecting claims 6-13 and 25 over Hagberg I alone is reversed.

3. The examiner's rejection based on Bisacchi, Slusarchyk, Searcey and Hagberg II

The examiner rejected claims 20-21 as being unpatentable under 35 U.S.C. § 103 over Bisacchi, Slusarchyk, Searcey and Hagberg II. This rejection is reversed for the same reason that the rejection of claims 6-19 and 22 over Bisacchi, Slusarchyk and Searcey was reversed. The information contained in Hagberg II does not overcome the deficiencies of the combination of Bisacchi, Slusarchyk and Searcey.

4. The examiner's rejection based on Hagberg I, Bisacchi, Slusarchyk and Hagberg II

The examiner rejected claims 14-22 as being unpatentable under 35 U.S.C. § 103 over Hagberg I, Bisacchi, Slusarchyk and Hagberg II. This rejection is reversed for the same reason that the rejection of claims 6-13 and 25 over Hagberg I alone was reversed.

5. New grounds of rejection

Appeal No. 95-0865  
Application 08/08/007,950

Pursuant to 37 CFR § 1.196(b), we enter the following new grounds of rejection.

a. General observations concerning new grounds of rejection based on the prior art

In making the following prior art rejections, we note that applicants' use known starting materials to obtain a known product having a known utility. The claims are directed to a process, not products. Each of the process steps claimed by applicants involves the use of known organic synthesis techniques.

We have not overlooked arguments made in applicants' Appeal Brief. Applicants maintain that there is an issue of whether a person having ordinary skill in the art would have selected a 6-halopurine from the various purines described by Bisacchi (Appeal Brief, page 15). There are at least two answers to applicants' argument. First, Bisacchi describes only four specific 6-substituted purines, one of which is 2-amino-6-chloropurine (col. 7, last line to col. 8, first line). Second, applicants' process is one for making a known compound from known starting materials and Bisacchi describes the known starting materials and the known final product. We believe that a person having ordinary skill in the art, seeking to make the compound applicants make, would have found it obvious to start with

Appeal No. 95-0865  
Application 08/08/007,950

2-amino-6-chloropurine, among other compounds, to make the compound applicants make.

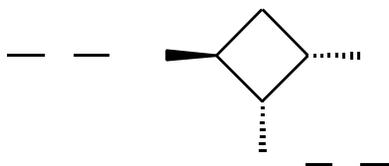
Applicants further argue (Appeal Brief, pages 15 and 16) that there would have been no motivation to select the tetraalkylammonium salt described by Searcey in place of the known alkali salts. On this record, we disagree for the reasons given in connection with our explanation of the rejection of claim 25, infra.

Applicants still further argue (Appeal Brief, pages 15 and 16-17) that one would not expect an increase in yield (as described by Searcey) in the process of Bisacchi or Slusarchyk. Again, there are at least two answers to applicants' argument. First, applicants' claims do not require an increased yield. In fact, applicants' specification does not set out a prior art problem which is solved by the claimed process. Second, we disagree that there is no expectation of success when a purine in its tetraalkylammonium salt form is used. Example 10 of Hagberg I demonstrates quite the contrary. Moreover, given the rather compelling improved yield results described by Searcey, we believe that a person having ordinary skill in the art would have reasonably expected improved yields when a purine in its tetraalkylammonium form is reacted with a halo-containing compound to attach the compound to the purine at the 9-position.

Appeal No. 95-0865  
Application 08/08/007,950

b. Claim 25

Claim 25 is rejected under 35 U.S.C. § 103 over Slusarchyk and Searcey. Claim 25 is not a model of clarity due to its use of Z and Z<sub>1</sub>. Nevertheless, we believe claim 25 calls for reacting 6-halo-purine in its tetraalkylammonium salt form with a compound having the formula Z<sub>1</sub>) X, including, inter alia, cyclobutanes having the formulae:



and



where:

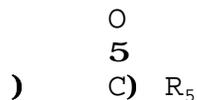
(1) X is a leaving group selected from the group consisting of:

Appeal No. 95-0865  
Application 08/08/007,950

- (a) chloro, bromo, iodo,
- (b) an aryl sulfonyloxy group,
- (c) a substituted alkyl sulfonyloxy group,
- (d) a nitro-substituted benzene sulfonyloxy group, and
- (e) fluorosulfonyloxy, and

(2) "P" or "Prot" is a protecting group ( $Z_1$ ) selected from the group consisting of:

- (a) t-butyldimethylsilyl,
- (b) t-butyldiphenylsilyl,
- (c) (tri-phenylmethyl)dimethylsilyl,
- (d) methyldiisopropylsilyl,
- (e) triisopropylsilyl,
- (f) benzyl,
- (g) p-methoxybenzyl,
- (h) trityl,
- (i) 4-monomethoxytrityl,
- (j) 4,4'-dimethoxytrityl and
- (k) acyl groups of the formula



wherein  $R_5$  is

- i) straight or branched chain alkyl of 1 to 6 carbon atoms or
- ii) phenyl.

Slusarchyk differs from the invention defined by claim 25 in that Slusarchyk does not describe the use of the purine in its tetraalkylammonium salt form. Rather, Slusarchyk describes the

Appeal No. 95-0865  
Application 08/08/007,950

use of purines in their alkali salt forms. We also note that Slusarchyk describes the use of only the 3-monosubstituted cyclobutanes. See Compound 2 (page 5). The Slusarchyk leaving group X is described as being selected from the group consisting of chloro, bromo, iodo, an aryl sulfonate (e.g., p-toluenesulfonyloxy) or an alkyl sulfonate (e.g., methanesulfonyloxy (mesyl)) (page 5, lines 20-21).

Searcey describes the reaction of nitro-imidazoles with halo containing compounds and indicates that better yields are obtained when the nitro-imidazole is reacted in its tetraalkylammonium salt form than when reacted in its alkali salt form. To be sure, an imidazole is not the same as a purine. However, the similarities between Searcey's imidazole and Slusarchyk's purines are apparent upon review of their respective structures:



Appeal No. 95-0865  
Application 08/08/007,950

The imidazole is shown on the left and the purine on the right. Both Slusarchyk and Searcey react halo-containing compounds with their respective imidazoles or purines at the N) H position.

What Searcey tells us is that if the tetraalkylammonium salt form of the imidazole is used when reacting with a halo-containing compound, better yields are obtained vis-à-vis an alkali salt form of the imidazole. The use of an alkali salt for of a purine is known as shown by Slusarchyk. Based on the teachings of Searcey, we are of the opinion that one skilled in the art would have recognized that the principles of Searcey would be applicable to purines as well as imidazoles.

We have not overlooked applicants' argument that there is "no indication [in Searcey] that the use of tetraalkylammonium salts will be of benefit in reactions beyond those disclosed" (Appeal Brief, page 16). It is true that there is no explicit recognition of any benefit beyond nitro-imidazoles. However, Searcey and Slusarchyk are attempting to add a moiety at the same point, i.e., the N) H in the diagram set out above. We believe one skilled in the art would recognize that the technique of Searcey would be expected to have applicability beyond mere nitro-imidazoles. Moreover, we need not bottom our obviousness rationale on improved yields. While improved yields may well be

Appeal No. 95-0865  
Application 08/08/007,950

expected in light of Searcey when the tetraalkylammonium salt form of a purine is used, it would not make any difference to our decision if no improved yield were obtained. The fact is applicants do not describe any advantage vis-à-vis the prior art for the claimed process in their specification. While an advantage need not be described in order to establish patentability, the absence of a stated problem and solution mean that any cogent reason for combining the teachings of Searcey and Slusarchyk suffices to establish obviousness. The improved yields described by Searcey provide a cogent reason--it simply cannot be argued in this day and age, consistent with common sense, that organic chemists do not seek improved yields. Hence, we believe that a person having ordinary skill in the art would have found it obvious to use Searcey's process in the purine art and reasonably would have expected success in using Searcey's process to add a moiety at the 9-position of the purine.

c. Claim 6

Claim 6 is rejected as being unpatentable under 35 U.S.C. § 103 over Bisacchi, Slusarchyk, Searcey, Hagberg I, **Ichikawa**, European Patent Application 0 358 154 (published March 14, 1990) and **Zahler**, European Patent Application 0 458 363 (published November 27, 1991).

Appeal No. 95-0865  
Application 08/08/007,950

The reason we reversed the examiner's rejection of claim 6 based on Bisacchi, Slusarchyk and Searcey was the absence of any teaching in Searcey that the use of the tetraalkylammonium salt form would serve in reactions with compounds beyond those containing a halo group. The deficiency we found in the examiner's rejection, however, is cured by a reference already in the record, namely, Hagberg I, Ichikawa and Zahler. Whereas Searcey reacts an imidazole in the tetraalkylammonium salt form with a compound containing a halo group, Hagberg I teaches reaction of a purine in the tetraalkylammonium salt form with a compound containing mesyl group. See Example 10 of Hagberg I (page 33). Furthermore, Hagberg I teaches that the "leaving" group  $X^2$  (see Compound XIII, page 16) can be chloro, bromo, iodo or  $SO_2R^2$  (page 13, lines 18-19) where  $R^2$  can be (page 9, lines 21-24):

- (1) alkyl containing 1-8 carbon atoms (e.g., mesyl);
- (2) fluorinated alkyl containing 1-8 carbon atoms, such as trifluoromethyl (triflyl);
- (3) alkylaryl such as benzyl, or
- (4) aryl such as unsubstituted for substituted phenyl.

Appeal No. 95-0865  
Application 08/08/007,950

Given that Hagberg I treats his various X<sup>2</sup> groups as interchangeable and describes the use of the alkyl group mesyl as working with the tetraalkylammonium salt form of a purine, we are of the opinion that a person having ordinary skill in the art would have recognized that compounds containing any of the X<sup>2</sup> groups listed by Hagberg I, including halo, mesyl and triflyl, would react with purines in the tetraalkylammonium salt form. Also teaching the interchangeability of halogen, mesyl and triflyl leaving groups in an analogous reaction is Ichikawa. Specifically, Ichikawa describes the reaction of (1) a cyclobutane (Compound V--page 5) having an X leaving group which can be, inter alia, halogen, triflyl or mesyl (page 5, lines 43-45) with (2) a purine (e.g., Compound XIV--page 6) to make Compound IV (page 3) where B can be 2-amino-(Y<sub>3</sub> is amino)-6-chloro-(Y<sup>2</sup> is halogen)-purine (page 4, line 15, left formula).

In light of the organic synthesis techniques described collectively by Searcey and Hagberg I, we believe that one skilled in the art would recognize that a tetraalkylammonium salt form of either an imidazole or a purine could be reacted with a compound containing either a halo group (Searcey) or a mesyl group (Hagberg I).

Our conclusion that the subject matter of claim 6 (as well as other claims) would have been obvious is reinforced by Zahler.

Appeal No. 95-0865  
Application 08/08/007,950

Zahler describes the reaction of purines with cyclobutanes. Zahler specifically describes the reaction of (1) a cyclobutane Compound 2 (page 9) having a leaving group which may be, inter alia, mesyl, triflyl or nosyl (page 9, lines 24-25) with (2) a purine Compound 3 (also page 9) to make (3) a 9-disubstituted-purine (Compound 4) using either potassium carbonate, sodium hydride or potassium hydride (page 9, line 43) or Compound 3 in its tetraalkylammonium salt form (page 10, lines 19-21). Zahler also describes making a 9-disubstituted cyclobutane-6-chloro-2-amino-purine (Compound 6--page 11) "under conditions analogous to those used in making the preparation of compound 4" (page 11, lines 12-13).

In light of our discussion above, a person having ordinary skill in the art would have found it obvious to react applicants' purine in its tetraalkylammonium salt form with a bis (2,3-protected hydroxymethyl) cyclobutane having an X group which is a perfluoroalkane sulfonyloxy group, such as triflyl. It follows that the subject matter of claim 6 includes subject matter which would have been obvious within the meaning of 35 U.S.C. § 103.

d. Claim 7

Appeal No. 95-0865  
Application 08/08/007,950

Claim 7 is rejected as being unpatentable under 35 U.S.C. § 103 over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler.

Claim 7 is believed to be unpatentable for the same reasons that Claim 6 is unpatentable. Bisacchi describes R<sub>4</sub> "protecting" groups which are the same as applicants' claimed Prot groups (col. 3, lines 59-63). The use of a cyclobutane wherein X is trifluoromethanesulfonyloxy has already been discussed. Bisacchi (col. 7, last line), Slusarchyk (page 7, Compound 14) and Hagberg I (page 16, line 10 where R<sup>7</sup> is chloro) describe the use of compounds corresponding to applicants' compound wherein X<sup>1</sup> is chloro. Both Searcey (page 1312) and Hagberg I (Example 10) describe the use of tetrabutylammonium salt forms.

e. Claim 8

Claim 8 is rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler.

Claim 8 is believed to be unpatentable for the same reasons that Claims 6 and 7 are unpatentable, it being further noted that Bisacchi describes an R<sup>4</sup> protecting group which is acetyl (col. 3, line 61) or benzoyl (col. 3, line 62).

f. Claim 9

Appeal No. 95-0865  
Application 08/08/007,950

Claim 9 is rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler.

Claim 9 is believed to be unpatentable for the same reasons that Claims 6-8 are unpatentable, it being further noted that Hagberg I describes the use of R<sup>7</sup> groups, corresponding to applicants' Y<sub>1</sub> group, which may be iodo (page 16, line 10; page 12, lines 1-3 referring to Y; page 10, line 1 referring to X<sup>1</sup>; and page 9, lines 19-20 wherein X<sup>1</sup> can be "iodine (sic--iodo)").

g. Claim 10

We do not reject claim 10 because we have not been able to find anything in the combination of Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler which suggests the use of an ammonium salt wherein R<sub>4</sub> is benzyl. Our decision not to reject claim 10 under 37 CFR § 1.196(b) is without prejudice to the examiner citing and applying additional prior art which describes the use of an ammonium salt within the scope of claim 10.

h. Claim 11

Claim 11 is rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler.

Claim 11 is believed to be unpatentable for the same reasons that Claims 6-9 are unpatentable. Bisacchi describes (1)

Appeal No. 95-0865  
Application 08/08/007,950

the use of an R<sup>4</sup> protecting group which is benzoyl (col. 3, line 62, corresponding to applicants' Prot group; (2) the leaving group triflyl (col. 3, line 67), corresponding to applicants' X; and (3) 2-amino-6-chloropurine (col. 7, last line), which corresponds to applicants' Y<sub>1</sub> being chloro. As previously noted, both Searcey and Hagberg I describe the use of tetrabutylammonium salt forms corresponding to applicants' R<sub>1</sub> through R<sub>4</sub> being n-butyl.

i. Claim 12

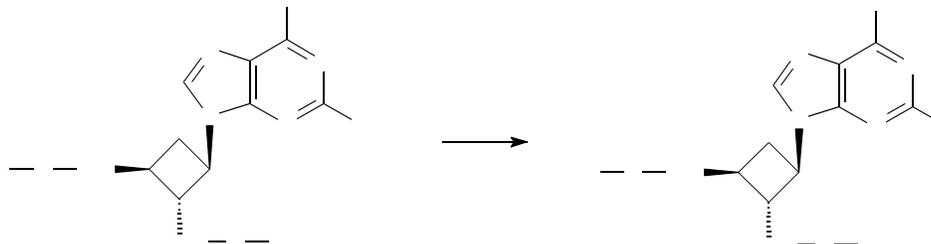
Claim 12 is rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler.

Claim 12 is believed to be unpatentable for the same reasons that Claims 6-9 and 11 are unpatentable, it being noted that Bisacchi describes the use of a leaving group X which can be p-nitrobenzenesulfonyloxy (nosyl) (col. 4, lines 30-31).

j. Claim 13

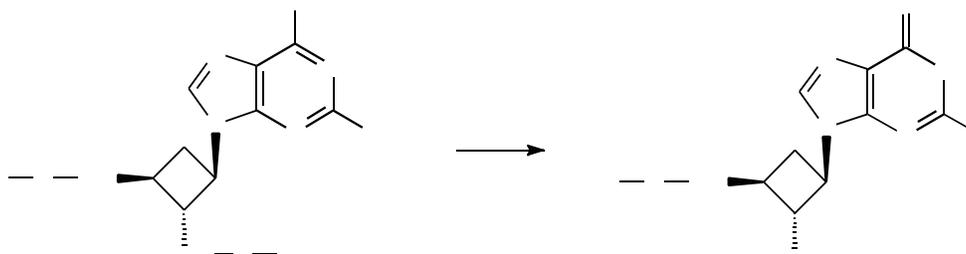
Claim 13 is rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler. Claim 13 requires two additional steps.

Step (b) involves treatment to remove the "Prot" protecting groups and replacement of those groups with hydrogen (H) groups. The reaction is shown schematically below:



Bisacchi contains an extensive discussion of the manner in which protective groups are removed (col. 8, line 17 through col. 10, line 14).

Step (c) involves treatment of the deprotected compound to convert the  $Y_1$  group from a chloro ( $\text{Cl}$ ) to an oxo group to produce the compound [1R-(1'',2 $\text{S}$ ,3'')]-2-amino-9-[2,3-bis(hydroxymethyl)-cyclobutyl]-1,9-dihydro-6H-purin-6-one according to the following reaction scheme:



Slusarchyk describes the conversion of a chloro-compound to an oxo-compound (page 8, lines 28-48).

Appeal No. 95-0865  
Application 08/08/007,950

The addition of steps (b) and (c) to what is otherwise basically the process of Claim 6 does not render Claim 13, as a whole, patentable over the prior art. A person having ordinary skill in the art would have wanted the oxo compound because it is a known active and useful compound (specification, page 1; Bisacchi, col. 1, lines 7-20). Steps (b) and (c), as shown by the prior art, are conventional organic synthesis techniques.

k. Claim 14

Claim 14 is rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler.

Claim 14 is believed to be unpatentable for the same reasons that Claim 13 is unpatentable.

Claim 14 requires that step (b) take place in the presence of a fluoride ion. Bisacchi describes the use of compounds which produce fluoride ions to accomplish deprotection (col. 8, lines 29-31 and 53-54; col. 9, line 47).

Step (c) of Claim 14 further requires acid hydrolysis. Slusarchyk describes the use of aqueous hydrochloric acid to accomplish conversion of the chloro group to an oxo group (page 8, line 28).

Appeal No. 95-0865  
Application 08/08/007,950

Applicants' claimed steps (b) and (c) would appear to involve use of well known organic synthesis techniques for their intended purpose.

l. Claim 15

Claim 15 is rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler. Claim 15 is believed to be unpatentable for the same reasons that Claims 13-14 are unpatentable. Claim 15 requires a "Prot" group which is benzyl and use of boron trichloride to accomplish deprotection. Bisacchi describes the use of R<sup>4</sup> protection groups which are benzyl and their deprotection using, inter alia, boron trichloride (col. 8, lines 35-44).

m. Claim 16

Claim 16 is rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler.

Claim 16 is believed to be unpatentable for the same reasons that Claims 13-15 are unpatentable. Claim 16 requires a "Prot" group which is acetyl and use of sodium methoxide in methanol to accomplish deprotection. Bisacchi describes the use of R<sup>4</sup> protection groups which are acetyl and their deprotection using, inter alia, sodium methoxide in methanol (col. 8, lines 44-50).

n. Claim 17

Claim 17 is rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler. Claim 17 requires the same two additional steps as Claim 13, but in reverse order. The order in which deprotection and conversion of the chloro group to the oxo group at the 6-position take place would not seem to be significant. In this respect, we call attention to Bisacchi (col. 8, lines 20-26) which teaches that (1) deprotection then chloro to oxo conversion or (2) chloro to oxo conversion followed by deprotection are optional orders for accomplishing both deprotection and chloro to oxo conversion.

o. Claim 18

We do not reject claim 18 because we have not been able to find anything in the combination of Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler which describes the use of hot aqueous acetic acid for conducting step (b). Our decision not to reject claim 10 under 37 CFR § 1.196(b) is without prejudice to the examiner citing and applying additional prior art which describes the use of hot aqueous acetic acid for accomplishing conversion of a chloro group to an oxo group at the 6-position of a purine.

p. Claim 19

Claim 19 is rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler. Claim 19 requires the same two additional steps as Claim 13, but in reverse order. The order in which deprotection and conversion of the chloro group to the oxo group at the 6-position take place would not seem to be significant. In this respect, we call attention to Bisacchi (col. 8, lines 20-26) which teaches that (1) deprotection then chloro to oxo conversion or (2) chloro to oxo conversion followed by deprotection are optional orders for accomplishing both deprotection and chloro to oxo conversion. The use of "hydrogenolysis" to deprotect R<sup>4</sup> groups is described by Bisacchi (col. 8, lines 36-44), particularly when the P protecting group is benzyl as required by Claim 19.

q. Claims 20-21

Claims 20-21 are rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler. Claim 20 is similar to Claim 13, but calls for a step (b) in which the "Prot" protecting groups are removed and the Y<sub>1</sub> group (e.g., a chloro) at the 6-position is converted to a 6-methoxy ( )OCH<sub>3</sub>) group. As is apparent from Claim 21, step (b) may be accomplished by treatment with sodium methoxide in methanol.

Appeal No. 95-0865  
Application 08/08/007,950

Bisacchi describes deprotection by treatment with sodium methoxide in methanol (col. 8, lines 44-50), particularly when the "Prot" group is benzoyl, as required by Claim 21. Slusarchyk reveals that conversion of a chloro group at the 6-position to an alkoxy group ( $\text{OR}_4$  in Slusarchyk) can be accomplished by known methods (page 9, last line through page 10, line 22).

Hagberg I describes hydrolysis of Compound III (page 9) containing an  $\text{X}^1$  group which can be, inter alia,  $\text{OR}^2$ , where  $\text{R}^2$ , inter alia, may be alkyl (e.g., methyl), in the presence of sodium hydroxide (page 9, line 27) to produce a "compound of the [Hagberg I invention" which, of course, is a purine compound with an oxo ( $\text{4O}$ ) at the 6-position (page 7, Compound I).

r. Claim 22--prior art rejection

Claim 22 is rejected as being unpatentable over Bisacchi, Slusarchyk, Searcey, Hagberg I, Ichikawa and Zahler. Claim 22 is narrower than Claim 6 in that it limits the "Prot" group to acyl. Claim 22 also requires a step (b) and a step (c).

Step (b) calls for (indentation and paragraph numbers added):

- (1) treating the product from part (sic--step) (a) with hot aqueous sodium or potassium hydroxide or

Appeal No. 95-0865  
Application 08/08/007,950

(2) treating the product of part (a) with an acid such as hydrochloric acid followed by sodium or potassium hydroxide and heat (sic--heating) to remove the protecting groups and convert the  $Y_1$  substituent to a 6-oxo \*\*\*.

Slusarchyk describes treatment of a product similar to that obtained in applicants' step (a) with hot aqueous hydrochloric acid to convert a chloro group in the 6-position to a 6-oxo group (page 8, lines 28-48).

Bisacchi describes treatment of a compound like the compound obtained in applicants' step (a) with potassium hydroxide to remove the  $R^4$  protecting groups, particularly when the  $R^4$  group is an acyl group (col. 8, lines 44-50).

Step (c) requires separating the desired product from the reaction mixture. Bisacchi describes obtaining a purified product through chromatography (col. 9, lines 21-22).

Applicants' steps (b) and (c) would appear to involve conventional techniques for removing protecting groups and converting a chloro group in the 6-position to a 6-oxo group and separating to obtain a desired product.

s. Claim 22--indefiniteness rejection

Appeal No. 95-0865  
Application 08/08/007,950

Claim 22 is rejected under the second paragraph of 35 U.S.C. § 112 as being indefinite. The limitation which is indefinite is "an acid such as hydrochloric acid \*\*\*." The language "such as hydrochloric acid" does not limit Claim 22 because the claim otherwise reads on the use of any "acid." Moreover, it is unclear as to whether applicants claim an "acid" or only "hydrochloric acid." As a general proposition, we believe that every word in a claim should be capable of having some limiting significance. The words "such as hydrochloric acid" would not appear to limit Claim 22. If an applicant can use the language "such as hydrochloric acid," it follows that the applicant could also recite "such as hydrochloric acid" followed by an extensive list of other acids, all of which would serve to make claims difficult to understand and/or interpret. Consistent with all of the paragraphs of 35 U.S.C. § 112, the proper manner to claim both "acid" and "hydrochloric acid" is to present one claim to "acid" and another (perhaps dependent) to "hydrochloric acid."

### **C. Decision**

The examiner's prior art rejections are reversed.

Claims 6-9, 11-17, 19-22 and 25 have been rejected pursuant to 37 CFR § 1.196(b) as being unpatentable under 35 U.S.C. § 103 over the prior art.

Appeal No. 95-0865  
Application 08/08/007,950

Claim 22 has been rejected pursuant to 37 CFR § 1.196(b) as being indefinite within the meaning of the second paragraph of 35 U.S.C. § 112.

**D. Further observation**

We have expressly indicated why Claims 10 and 18 have not been rejected. If applicants are aware of any prior art which would overcome our stated reasons for not rejecting either Claim 10 or Claim 18, applicants (or their attorneys) should make the examiner aware of that prior art. 37 CFR § 1.56. Apart from any obligation of applicants to inform the examiner of any prior art mentioned in the preceding sentence, should the examiner be aware of any such prior art, the examiner should feel free to make a rejection of Claims 10 and/or 18. In short, nothing in this opinion should be treated as precluding the examiner from making a rejection of Claims 10 and/or 18 (or any other claim) based on additional prior art not mentioned in this opinion.

**E. Time for taking action**

This opinion contains a new ground of rejection pursuant to Rule 196(b) (37 CFR § 1.196(b), amended effective Dec. 1, 1997). See Notice of Final Rule, 62 Fed. Reg. 53131, 53197

Appeal No. 95-0865  
Application 08/08/007,950

(Oct. 10, 1997), reprinted in 1203 Off. Gaz. Pat. & Trademark Office 63, 122 (Oct. 21, 1997)).

Rule 196(b) provides that, "A new ground of rejection shall not be considered final for purposes of judicial review."

Rule 196(b) also provides that the applicant, **WITHIN TWO MONTHS FROM THE DATE OF ENTRY OF THIS DECISION**, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of proceedings (§ 1.197(c)) as to the rejected claims:

(1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner. . . .

(2) Request that the application be reheard under § 1.197(b) by the Board of Patent Appeals and Interferences upon the same record. . . .

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

Appeal No. 95-0865  
Application 08/08/007,950

**REVERSED**

(37 CFR § 1.196(b))

\_\_\_\_\_  
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Administrative Patent Judge )  
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WILLIAM F. SMITH, )  
Administrative Patent Judge )  
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Appeal No. 95-0865  
Application 08/08/007,950

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