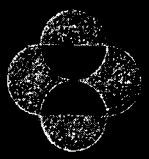


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NOTEBOOK PROCEDURE*

This notebook is the property of Merck and Co., Inc. and will contain confidential, proprietary, and trade secret information. The notebook records are important legal documents essential for obtaining patent protection on inventions and federal approval for our product applications. It is assigned to you, remains your responsibility while in your possession, and should be retained on Merck premises except when required for conducting business or experiments on non-Merck premises or when transporting it between Merck buildings. Should you transfer to another Department or Division, this notebook and all ancillary data related to the experiments in it must be returned to the closest Research Information-MRL (RI) site for disaster protection; if required again, it can be charged out to anyone with legitimate need. All incomplete notebooks will periodically be protected by microfilming or optical scanning, according to a schedule maintained by RI. This notebook will serve as a primary source of experimental results. However, the use of a notebook is not restricted to experimental work, but includes all matters for which a readily identifiable, properly witnessed, and dated record may be useful (government regulations, litigation, patent purposes, *etc.*). To assure that this notebook is a useful document, follow these procedures:

- 1) Enter directly in this notebook all your objectives, ideas, experimental plans, experimental data, observations, calculations, *etc.* Do not put data on loose sheets and then transcribe them to this book.
 - 2) Make all entries in dark, indelible ink, preferably black, using a pen which creates an impression (*e.g.*, ballpoint).
 - 3) All entries should be from a single author; entries by others should be clearly identified.
 - 4) Erasures, whiting out, writing over, taping over, or pasting over are not permitted. Make corrections by lining out with a single line (do not obliterate entry), initialing, dating, and explaining.
 - 5) All entries must be made in the notebook at the time of the experiment. The date of each recorded experiment must be entered in the notebook using a non-ambiguous Merck Standard format (*e.g.*, 15 Dec. 1997). Each day's entries must be signed and dated by the user immediately below the last entry. The signature should include first name, initial, and surname (or what is commonly used by the investigator on legal documents); when multiple entries are made on different dates, each entry should be dated and signed.
 - 6) Write on both left- and right-handed pages of the book. Include all observations, notes, references, quotations, discussions, calculations, sketches, *etc.*
 - 7) In recording experiments, clearly identify by appropriate reference: starting materials, end products, protocols, controls, results, conclusion, cross-references, *etc.*
 - 8) The record must be continuous so that no suspicion of interpolation, falsification, or amendment can be aroused. Accordingly, all entries must be made consecutively with no blank pages. Vacant spaces on a page should be marked out with a diagonal line or an "X", dated, and initialed. All entries related to previously numbered and paginated experiments must be designated by a reference in the margin.
 - 9) Each page must be countersigned by someone not likely to be a co-inventor but who understands the significance of the recorded experiments. Countersigning should be done within one month, not to exceed three months, after the completion of the experiment. **NOTE:** If the Standard Operating Procedure (SOP) for the experiment specifies the frequency of countersignature, countersignature should follow that SOP consistently (*e.g.*, if the SOP states that counter-signature will occur at the completion of each experiment, then it should occur one time at the end of each experiment; if the SOP states weekly countersignature will occur, then countersignature should be accomplished weekly). Any SOP developed by the laboratory for countersignature must also comply with the one month, not to exceed three month rule.
 - 10) Any essential ancillary records such as photographs, computer printouts, spectra, graphs, memos, technical reports, *etc.* which may substantiate or validate your notebook should be referenced to the notebook number and page and be kept together as a reference to that notebook. A reference to the ancillary data should also be entered on the notebook page.
 - 11) Complete a Table of Contents or index to enable ready access in the future by yourself or others. Pages are provided for this purpose in the front of the book. Index pages for unbound notebooks may be obtained from RI.
- The records must be maintained in compliance with your written departmental procedure on keeping laboratory notebooks.

*Complete instructions are in MRL Policies, Procedures and Charters Manual, Policy 23, "Writing and Maintaining Laboratory Records", available from Research Information, MRL.

October, 1999

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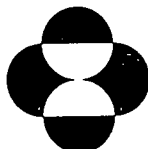
NOTEBOOK NUMBER: 72471

ASSIGNED TO:

Print K. J. B. Hinson

Signature [Handwritten Signature]

DATE: 19 Mar 2002



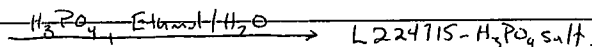
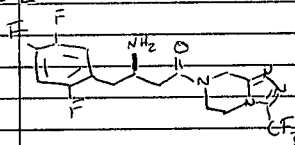
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LABORATORY NOTEBOOK

Salt Form, Crystallization & Isolation of L224715-H₃PO₄ salt

22 March 2002 Continued From



Reagents:		Fw	Am't	notes	ESH 22-2002
L224715 Ethanol Filter 72471-001		407	459g in 7.3L Ethanol	1.12	1.0
	72471-006	407	474g in 7.1L Ethanol	1.16	1.0
H ₃ PO ₄	Aldrich EO 1922880 85% in H ₂ O	98	291g	2.52	1.1
Ethanol	RM 107677				
Water	GMP		1.4 liters		

Procedure: Concentrated Ethanol solution of 72471-001 in unene on Rotovap Replaces 7 @ 30 mm Hg & 31°C bath. Added to Flasks 72471-006. Concentrated to thick golden oil. 2 liters of Ethanol was charged & oil was redissolved. The 2 liter soln was transferred via micron line filter to a 50 liter RBF equipped with stirrer, N₂ inlet & thermocouple & rinsed with GMP H₂O & Ethanol - usually clear. The Rotovap flask was rinsed with 1.25 liters of Ethanol & this was transferred to the vessel via same filter. The soln was heated to 67°C. 291g of H₃PO₄ was dissolved in 1 liter of GMP H₂O & transferred to a 5 liter addition funnel (clean by usual). The line filter used to transfer the soln was also rinsed with an additional 0.4 liters of H₂O into the add funnel the soln was mixed & then added to the ethanol soln over 15 minutes. Temperature dropped to 64°C and a slight white haze developed which was solids. The temperature was raised to 67°C for 0.5 hrs then cooled to 63°C. 6.00g of 70316-081 was added to the soln @ 62°C & seed bed formed & this was aged for 1.5 hrs @ 63°C. The batch was then cooled to 20°C over 12 hours.

23 March 2002 Slurry of solids which are crystals under microscope. Added 23.0 liters of Ethanol through a micron line filter over 2.5 hrs. After 1/2 hour with Ethanol present [715] = 1.51 g/L in filtered supernatant. Aged an additional 0.5 hrs then filtered batch washed 2 x 2.5 liters of Ethanol. Covered with shrink disk paper & dried under N₂ sweep over weekend.

25 March 2002 transferred to tared plastic bag 1057g of white salt isolated. H-NMR shows no ethanol - very clean 92% yield for crystallization.

Continued On.

Countersigned

 27-Mar-2002
 Date

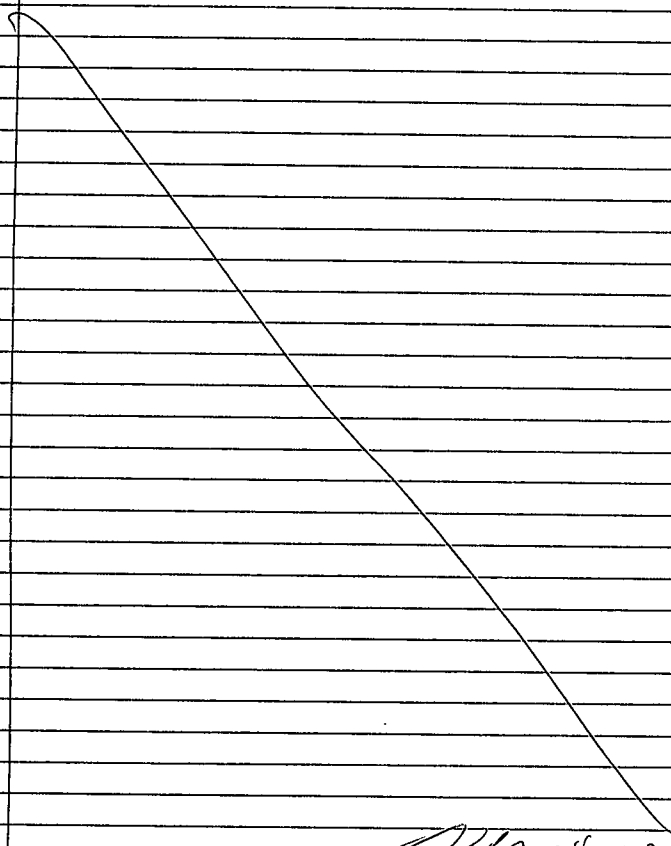


2002
Continued From:

28 Mar 2002 Yield is 79.5% over 4 steps from Beta lactam.

1057g	H ₂ PO ₄ salt	100% LCAP →	80.6 wt. Free base	8519g	91% Recovery
22.5kg	ML's	1.46 mg/L	→	32.8g	35%
4.1kg	wash	0.42 mg/L		1.7g	0.2

Subdivided 455g of material & then carried balance onto 72471-017
FBI 25 Mar 2002 79.7% mesbline



[Handwritten signature]

Continued On:



Continued
[Handwritten signature]
Date 22-MAR-2002

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