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NOTEBOOK PROCEDURE*

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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. Counter-signing 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. I B Hansen

Signature [illegible]

DATE: 19 Mar 2002

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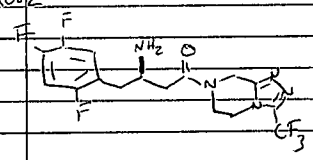
LABORATORY NOTEBOOK

Salt Form, Crystallization & Isolation of L224715-H_3PO_4 salt

22 March 2002 Continued From



$\xrightarrow{H_3PO_4,\ \text{Ethanol}/H_2O}$ L224715-H_3PO_4 salt.

Reagents:			FW	Amt	Moles ~~Mass~~	eqs
L224715	Ethanol filtrate 72471-001		407	459g in 7.3L EtOH	1.12	1.0
	72471-006		407	474g in 7.1L EtOH	1.16	1.0
H_3PO_4	Aldrich EO 1922880	85% in H_2O	98	291g	2.52	1.1
Ethanol	RM 107677					
Water	GMP			1.41 liters		

Procedure: Concentrated Ethanol solution of 72471-001 in vacuo on Rotovap Reeplab 7 @ 530 mm Hg & 31°C bath. Added to Flask E72471-006. Concentrated to thick golden oil. 2 liters of Ethanol was charged & oil was redissolved. The 2 liter soln was transferred via 1 micron line filter to a 50 liter RBF equipped with stirrer, N_2 inlet & thermocouple & rinsed with GMP H_2O & Ethanol - usually clean. 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 H_3PO_4 was dissolved in 1 liter of GMP H_2O & transferred to a 5 liter addition funnel (clean by usual). The line filter used to transfer the soln was ~~etc~~ rinsed with an additional 0.4 liters of H_2O 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 70314-081 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 stellate under microscope. Added 23.0 liters of Ethanol through a 1 micron line filter over 2.5 hrs. After ½ hour with Ethanol present [715] = 159 mg/g in filtered supernatant. Aged an additional 0.5 hrs then filtered batch. Washed 2 x 2.5 liters of Ethanol. Covered with shrink stick paper & dried under N_2 sweep over weekend.

25 March 2002 transferred to tared plastic bag. 1057g of white salt isolated. ^{1}H-NMR shows no ethanol - very clean. 92% yield for crystallization

Continued On.

Countersigned
27-mar-2002
Date

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Continued From:

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

1057g	H_3PO_4 salt	100% LCAP →	80.6 wt% Free base	851.9g	9% Recovery
225.5kg	ML's	1.46 mg/g →		32.8g	3.5%
4.1kg	wash	0.42 mg/g		1.7g	0.2
					94.7% mass balance

Sub divided 455g of material & then carried balance onto JO 72471-017

25 Mar 2002

Continued On:

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22-MAR-2002

Date

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