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DIRECCIÓN DE NUEVAS CREACIONES**

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Abogado
EMILIO FERRERO

ASUNTO	Radicación	07 117167
	Trámite	11
	Evento	379
	Actuación	519
	Oficio	05560
	Folios	7

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (Fase Nacional)	☒	Capítulo I	☒
		Capítulo II	☐
No. Solicitud Internacional	PCT/EP2006/062008		
Fecha de Presentación Internacional	03/Mayo/2006		

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 35 a 49	06/Noviembre/2007
Reivindicaciones:	Folios 50 a 51	06/Noviembre/2007
Dibujos:	Folios 53 a 55	06/Noviembre/2007
Prioridad:	DE 10 2005 021 056.2	6/Mayo/2005

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Proceso para aislar metilglicininitrilo-N,N-diacetonitrilos de una mezcla cruda acuosa"

El problema planteado en la actual solicitud consiste en la necesidad de un proceso que permita aislar el intermediario metilglicininitrilo-N,N-diacetonitrilo (MGDN) del medio de reacción como una sustancia pura, con el fin de lograr altos rendimientos de MGDA.

Expediente 07 117167 1er Art 45

Para efectuar la separación de MGDN dentro de la solicitud en estudio se propone un método de aislamiento efectuado en un cristizador que comprende

- a) Enfriamiento de la emulsión obtenida en la reacción hasta una temperatura menor a la temperatura de solidificación de la emulsión a una tasa de enfriamiento promedio $\leq 5\text{K/h}$, hasta que sustancialmente todo el MGDN emulsificado se ha solidificado
- b) La suspensión acuosa obtenida en la etapa a) continua enfriándose y/o concentrándose y la tasa de enfriamiento es $\geq 5\text{K/h}$

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07C 253/034.

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

En general se observan problemas de redacción en todo el texto, tanto en la descripción como en las reivindicaciones, probablemente debidos a una traducción deficiente del texto original. Se sugiere que solicitante presentar a esta Oficina una mejor traducción de la solicitud.

El capítulo reivindicatorio no es claro ni conciso dado que según la descripción, la invención está caracterizada por 2 etapas a) solidificación de MGDN emulsificado y b) Cristalización del MGDN remanente en solución. Se describen 3 posibles metodologías para la cristalización (etapa b) denominadas:

- Cristalización enfriante al vacío con reflujo total.
- Cristalización evaporativa isotérmica (sin reflujo)
- Emplear sucesiva o simultáneamente las dos anteriores con reflujo parcial.

Caracterizadas por aplicación de vacío y condiciones de reflujo. Dichas características y variaciones de la invención no están mencionadas o suficientemente divulgadas en las reivindicaciones. Se sugiere corregir esta inconsistencia entre la descripción y las reivindicaciones modificando la descripción o las reivindicaciones para que concuerden.

Con el objetivo de esclarecer el alcance de las reivindicaciones se sugiere evitar el uso de expresiones imprecisas y no limitativas dentro del capítulo reivindicatorio, tales como:

- 1- "no excede"
- 2- "hasta que sustancialmente"
- 3- "se enfría además"
- 4- "puede ser mayor que"
- 5- "por debajo de"
- 6- "por lo menos"

Reemplazar las mencionadas expresiones por rangos específicos de t , T o tasa de enfriamiento, según corresponda, para los cuales el procedimiento es efectivo.

Particularmente se sugiere la revisión de ciertas reivindicaciones que carecen de claridad y especificidad en sus características

Expediente 07 117167 1er Art 45

La reivindicación 1 que carece de claridad porque se realizan dos caracterizaciones:

Un proceso para aislar (MGDN) de una emulsión acuosa **"que comprende"** MGDN y que tiene un contenido de MGDN de 3 a 50% en peso en un cristizador, **"que comprende"** las etapas de:

Esta manera de redactar no es apropiada y le resta claridad a la solicitud. Se recomienda al solicitante realizar las correcciones respectivas, definiendo el método o proceso de reclamado únicamente por las características que definen los procesos, (etapas, intermediarios involucrados, condiciones etc...) eliminando las características del MGDN del alcance de la reivindicación.

Las reivindicaciones 2 y 3 no son claras porque emplean el término "mezcla acuosa" el cual no había sido previamente descrito en la reivindicación independiente. Se sugiere emplear los mismos términos usados en la reivindicación uno respecto a la mezcla que se desea separar. Además cada una de estas reivindicaciones hace referencia a una etapa del proceso descrito en la reivindicación 1 pero estas no se

define mediante las condiciones específicas en que deben realizarse. No se establecen apropiadamente las condiciones en las que la etapa de "evaporación y/o remoción de calor" o la de "enfriar o concentrar" son realizadas, tales como presión, tiempos, temperaturas y condiciones de reflujo.

La reivindicación 4 no es clara porque hace referencia a una variación de la etapa b) descrita de manera incompleta en la reivindicación 1 y no establece apropiadamente los límites de aplicación de dicha variación. Se sugiere describir más detalladamente las condiciones de remoción del calor por vía de la pared del cristizador, restringiendo las condiciones a un rango razonable que se encuentre soportado en la descripción y corregir la expresión "pared del cristalización".

La reivindicación 7 no es clara porque en ella se emplea la expresión "La mezcla cruda" el cual no había sido previamente descrito en la reivindicación independiente (1). También le resta claridad el uso del nombre "metilglicinoitrilo" que difiere de utilizado en la descripción "alaninanitrilo" favor emplear la misma terminología a lo largo de toda la solicitud. Además el contenido de esta reivindicación no se encuentra soportado en la descripción, porque no se proporciona prueba del efecto técnico del proceso de purificación sobre una mezcla producida como se divulga en la reivindicación 7.

Descripción (Art 28 D 486)

La Descripción no es clara porque presenta falencias recurrentes en la redacción o traducción. Se requiere al solicitante Presentar a esta Oficina una mejor traducción de la solicitud.

Particularmente, Folio 35 líneas 20 y 26, Folio 39 línea 16 y párrafo 4, Folio 40 párrafo 1, folio 44 párrafo 2.

1. El símbolo **PH** no es el aceptado en el campo técnico de química al cual pertenece la invención.

Por último la descripción no divulga la invención de manera suficientemente completa para que la persona normalmente versada en la materia pueda ejecutarla particularmente respecto a las condiciones de presión y rangos de temperatura en las que es aplicable la etapa a. Se sugiere completar dicha información con base a las condiciones que han sido probadas y en las que se obtiene el efecto técnico sustentado, sin ampliar la materia original de la presente solicitud.

5. Determinación del Estado de la Técnica

Fecha de Presentación de la Solicitud de Prioridad: Mayo 6 del 2005 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación*
D1	US 5786313	Use of glycine-N,N-diacetic acid derivatives as biodegradable complexing agents for alkaline earth metal ions and heavy metal ions and process for the preparation thereof	22/Diciembre/1994
D2	US 5849950	Preparation of glycine N,N-diacetic acid derivatives	15/Diciembre/1998
D3	Journal of Crystal Growth Vol. 166, Págs 971–975	Emulsion solidification of meta-chloronitrobenzene: purification and crystallisation	1/Septiembre/1996
D4	Furnis, B S et al., Longman Scientific and technical. Tercera edición. Pág 131-153.	Vogel's textbook of practical organic chemistry".	1956

D1 http://worldwide.espacenet.com/publicationDetails/biblio?DB=EPODOC&II=0&ND=3&adjacent=true&locale=en_gb&FT=D&date=19980728&CC=US&NR=5786313A&KC=A divulga (página 7, ejemplo1) la preparación de MGDA (también llamado alanina-N,N-diacético) a partir de alaninonitrilo y menciona la cristalización del derivado MGDN por enfriamiento a 10°C de la mezcla de reacción.

D2 http://worldwide.espacenet.com/publicationDetails/biblio?DB=EPODOC&II=0&ND=3&adjacent=true&locale=en_gb&FT=D&date=19981215&CC=US&NR=5849950A&KC=A divulga (página 5, ejemplo 3) la preparación de MGDA a partir de iminodiacetonitrilo y menciona la cristalización del intermediario de MGDN.

D3 <http://www.sciencedirect.com/science/article/pii/S0022024896000656> divulga un procedimiento para separar m-cloronitrobenzeno de una emulsión por enfriamiento a tasa fija (pág 1, columna2, regiones 22-23).

D4 <http://es.scribd.com/doc/29100308/Vogel-s-Practical-Organic-Chemistry-3rd-Ed> divulga (página 123-130) los métodos usuales de purificación de sólidos particularmente por recristalización que son de conocimiento del técnico medio en el campo de la química. En donde se describe la cristalización por enfriamiento (pág123), la importancia de la velocidad de enfriamiento (pág 129) y la existencia de una región de temperatura óptima para formar cristales (pág 130).

6. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en un proceso para Metilglicinanitrilo-N,N-diacetonitrilo (MGDN) de una emulsión acuosa (ver folio 50).

Comparación de las características técnicas esenciales , con las del Estado de la Técnica:				
Solicitud	D1	D2	D3	D4
Un proceso para aislar (MGDN) que comprende las etapas :	Proceso para producir MGDA que incluye el paso de cristalizar MGDN	Proceso para producir MGDA que incluye el paso de cristalizar MGDN	Proceso para cristalizar m-cloronitrobenceno	Generalidades de purificación de solidos
a) partiendo de una temperatura por encima del punto de solidificación, la emulsión acuosa se enfría a una temperatura por debajo del punto de solidificación, la tasa de enfriado promediada durante el tiempo no excede 50 K/h, hasta que sustancialmente la cantidad total de MGDN emulsionado se haya solidificado.	Enfriar la mezcla hasta 10°C no se menciona la tasa de enfriamiento	Dejar enfriar durante 4h	Enfriar con tasas de enfriamiento fijas	Permitir que la solución caliente se enfríe causando así que la sustancia disuelta se cristalice (pág 123, renglón11)
b) La suspensión acuosa resultante se enfría además y/o se concentra y la tasa de enfriamiento puede ser mayor que en la etapa a)				Se debe tener en cuenta que la velocidad la formación de cristales es inversamente proporcional a la temperatura; enfriar a muy bajas temperaturas puede obstaculizar la cristalización. (pág 129, renglones46-48).
				Se puede dar la oportunidad para formar cristales si se pasa a través de una región de temperatura óptima para la formación de cristales (pág 130, renglones 2-4)

Los documentos D1 y D2, Los documentos D1 y D2 corresponden a los documentos del estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulgan un procedimiento para producir MGDA a partir de alaninonitrilo (D1, pág 7, ejemplo 1) o iminodiacetonitrilo (D2, pág 5, ejemplo 3) que involucra el aislamiento del intermediario MGDN para usarlo en la etapa siguiente como una sustancia pura y muestran rendimientos respectivos de MGDN de 82% (D1) y 92%(D2).

La diferencia entre la invención, definida en la reivindicación 1, y los procesos divulgados en D1 y D2 consiste en que el proceso descrito en la invención propone una separación por enfriamiento en dos etapas con diferente tasa de enfriamiento.

El Efecto Técnico que logra incluir este enfriamiento en dos etapas es que se previene la formación de cristales pequeños (finos) de MGDN que posteriormente se aglomeran formando inclusiones de liquido e impurezas en su interior, dicho de otra manera favorece la formación cristales de mayor tamaño y más puros, como se demuestra con los números de color Hazen obtenidos (Ver folios 14 y 15)

De acuerdo con la lectura detallada de la descripción no se proporcionan soportes del efecto del proceso de asilamiento reivindicado en el rendimiento de MGDN ni

de MGDA (producto final) que permitan establecer si el mencionado proceso provee una mejora técnica respecto al estado de la técnica. D1 (82% MGDN) y D2 (92%MGDN.)

El Problema Técnico Objetivo de esta solicitud, consiste en: cómo modificar el proceso divulgado en D1 y D2 para aislar el intermediario metilglicinitrilo-N,N-diacetonitrilo (MGDN) del medio de reacción como una sustancia pura, con el fin de lograr altos rendimientos de MGDA

Sin embargo, las técnicas de purificación de sólidos como la cristalización son comúnmente empleadas para aislar o purificar sólidos en el campo de la química y los principios de dicha técnica han sido divulgados en muchos los textos de química básica por ejemplo D4 que muestra las generalidades de la técnica de cristalización /recristalización de sólidos aprovechando la dependencia de la solubilidad de algunos compuestos con la temperatura (pág 123); y divulga la importancia del control de las velocidad de enfriamiento (pág 129, último párrafo) y la existencia de una región de temperatura optima para la formación de cristales (pág 130).

El documento D3 por su parte, muestra una aplicación de las técnicas de cristalización para la separación de isómeros p- y m- cloronitrobenceno que se encuentran en una emulsión, por medio del enfriamiento de la mezcla a tasas fijas (pág 1, columna 2, renglones 22-23).

Teniendo en cuenta el estado de la técnica, la persona del oficio medianamente versada en la materia podría inferir sin mucho esfuerzo de su parte, que para aislar de manera más efectiva el intermediario MGDN podría modificar el proceso de enfriamiento propuesto en D1 o D2, de acuerdo a las enseñanzas de D3 o D4, que sugieren el especial control que debe hacerse sobre la velocidad de enfriamiento (D3 pág 1, columna 2, renglones 22-23) y la importancia de permitir que la mezcla alcance y permanezca en una región de temperatura optima para su cristalización (D4 pág 130, renglones 2-3) llegando así al objeto de la presente invención. Por lo anterior se considera que la invención es obvia a la luz de D1 con D3, D1 con D4, D2 con D3 ó D2 con D4.

Conclusión:

En consecuencia la reivindicación 1 y sus dependientes 2 a 7 no cumplen con el requisito de nivel inventivo.

7. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 5786313	1 – 7	Nivel inventivo
D2	US 5849950	1 – 7	Nivel Inventivo
D3	Journal of Crystal Growth Vol. 166, Págs 971–975	1 – 7	Nivel Inventivo
D4	Furnis. B S et al., Longman Scientific and technical. Tercera edición. Págs 131-153.	1 – 7	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
_____ **11 ABR. 2012**

Elaborado por: Laura Carolina Pardo. *OK*
Revisado por: Jacqueline Alfonso Roza.

Emulsion solidification of meta-chloronitrobenzene: purification and crystallisation

R.J. Davey^a, J. Garside^a, A.M. Hilton^{a,*}, D. McEwan^b, J.W. Morrison^b

^a Department Chemical Engineering, UMIST, P.O. Box 88, Manchester, M60 1QD, UK

^b ZENECA Fine Chemicals Manufacturing Organisation, Leeds Road, Macclesfield, M22 1SF, UK

Abstract

Emulsion crystallisation has been investigated in order to assess its potential use both in the material science context, as a means of particle preparation and in the context of new purification processes.

1. Introduction

Emulsion crystallisation has been investigated in order to assess its potential use both in the material science context, as a means of particle preparation and in the context of new purification processes. The latter is driven by the increasing need for flexible purification technologies that are both energy efficient and environmentally acceptable [1–3]. In principle the emulsion process has much to offer with low enthalpy requirements compared to distillation and low solvent use compared to traditional solvent recrystallisation. In addition no special chemical plant is needed hence offering low capital cost.

The use of emulsified systems as a technique for studying homogeneous nucleation is well known since the pioneering work of Turnbull [4] on metals and paraffins. Dispersion of a melt into discrete small volumes allows heteronuclei to be isolated in certain droplets and homogeneous nucleation to occur in the remainder. Generally it has been found that the

smaller the drop size the more difficult nucleation becomes [5].

2. Experimental procedure

For this study we have chosen to crystallise m-chloronitrobenzene (m-CNB), from two component mixtures with its para isomer (p-CNB). The system exhibits simple eutectic behaviour. In the experiments reported here, m/p mixtures of 90:10 and 75:25 have been emulsified above their melting points, at a weight fraction of 2% in water using the sulphated alkylthiolate surfactant, Tensagex (supplied by Hickson-Mann). At an overall concentration of 0.2 wt% Tensagex was found to have no effect on the phase diagram and stable oil-in-water emulsions were prepared with drop sizes in the range 5–10 µm (measured using a Polyvar-MET optical microscope). These were then crystallised by cooling at fixed rates. As expected, at these small drop sizes, the emulsions showed significant undercooling (typically 30–40°C). In order to overcome this problem

and perform crystallisations at fixed temperatures a simple seeding technique was used in which the emulsion was cooled to the desired crystallisation temperature and 1 mg/ml of pure m-CNB crystals added. The subsequent progress of crystallisation in terms of purity, yield and crystal form was monitored by sampling and use of GC (sensitive down to 0.02% m-CNB) and optical microscopy. An emulsion of composition 60.9% m-CNB was also crystallised (with m-CNB seeds), at 15°C where we would expect a mixture of pure p-CNB and eutectic to crystallise, yielding no overall purification. Crystallisation rates and overall purities and yields have also been measured at 28°C for 90:10 m-CNB:p-CNB emulsions with differing droplet diameter, organic weight fraction and emulsifier content.

3. Results

Table 1 shows the product purity after 90 min for two emulsion compositions crystallised at various temperatures compared to equivalent material crystallised in a single stage (with no partial melting), on a cold surface. In terms of purity, a single step emulsion crystallisation offers considerable improvement over its progressive freezing counterpart. Previous studies on the melt and solution crystallisation of m-CNB have shown that its para isomer is a power-

Table 1

The effect of crystallisation temperature on final crystal purity

Original droplet composition (m:p CNB)	Liquidus temperature (°C)	Crystallisation temperature (°C)	Final crystal composition (after 90 min) (% m-CNB)
90:10	41	30	99.7
		28	99.3
		24	98.2
		22	93.6
		22*	90.4
75:25	34	25	99.7
		23	98.4

Emulsion drop diameter 5–10 µm, 2 wt% organic phase, 0.2 wt% Tensagex.

* Equivalent data measured by the freezing of bulk melt onto a chilled surface.

ful crystallisation inhibitor [6] and that its presence in the crystallising environment induces a profound polar morphology in m-CNB crystals [7]. Observations of the physical form of the crystals here proved very surprising for, as Fig. 1 illustrates, these were always single crystals, at least an order of magnitude larger than the drop size and having polar morphologies typical of crystals grown from melts or solutions in the presence of p-CNB [6].

As crystallisation preceded the emulsion droplet

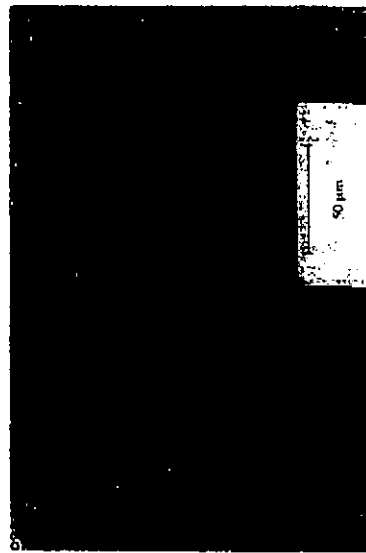


Fig. 1. Crystal of m-CNB growing from a 90:10 m-CNB emulsion at 22°C.

* Corresponding author.

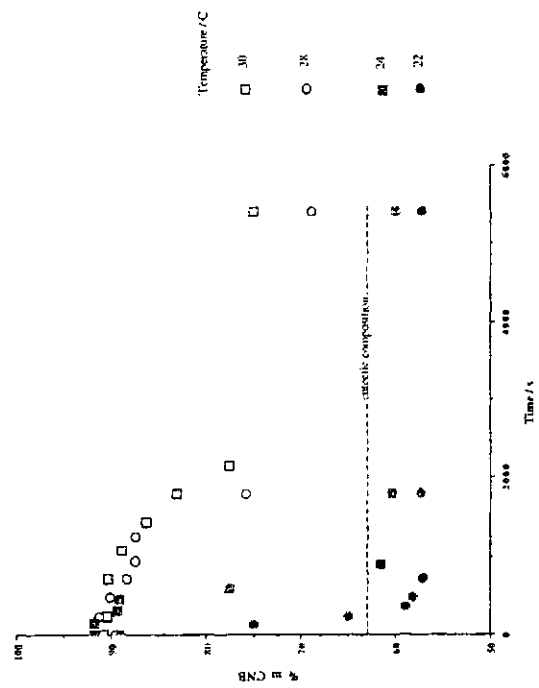


Fig. 2. Time dependence of emulsion droplet composition.

composition was measured as a function of time (total crystallisation times of 90 min). Liquid phase compositions of emulsions having initial m:p compositions of 90:10 crystallised at temperatures of 30, 27.1°C. At 30 and 28°C the final liquid phase com-

Table 2
The effect of droplet size, organic and surfactant weight fractions on final crystal purity, yield and emulsion composition

Droplet size (μm)	Organic weight fraction (%)	Surfactant weight fraction (%)	Purity (% m-CNB)	Yield Y_c (%)	Yield Y_s (%)	Final emulsion composition (% m-CNB)
20–50	2	0.20	95.43	71.81	80.96	66.79
5–10	2	0.20	94.29	68.05	76.68	68.84
3–5	2	0.20	94.23	67.55	76.13	66.69
5–10	10	0.80	97.88	86.81	97.34	66.08
5–10	4	0.34	96.23	70.11	79.05	67.08
5–10	2	2.00	99.49	68.20	76.98	68.94
5–10	2	0.10	90.29	68.51	73.85	68.84
5–10	2	0.01	95.01	89.01	100.00	64.75

90:10 m:p emulsions seeded at 28°C CNB.

Y_c is based upon the total mass of m-CNB used in the experiment.

Y_s is based upon the total crystallisable pure component calculated from the phase diagram using the lower rule.

positions are somewhat higher than expected from the phase diagram possibly because equilibrium had not been reached. At 24 and 22°C, however, while the liquid phase might be expected to have the eutectic composition it in fact has a composition richer in p-CNB. The final crystal purities were also measured (Table 1). The solid phase recovered from experiments performed at 24 and 22°C (below the eutectic temperature), have purities of 98.2 and 93.6% m-CNB respectively. Crystallisation of the 60.9% m-CNB emulsion at 15°C, contrary to expectations, yielded a final crystal purity of 65.5% m-CNB and a final liquid phase composition of 55.3% m-CNB.

An increase in organic weight fraction and/or droplet diameter has been found to increase crystallisation rates; this also being true when surfactant weight fractions are reduced. Overall crystal purity has been found to decrease slightly with increasing droplet size and increasing organic weight fraction while there appears to be an overall increase in purity with increasing surfactant concentration (Table 2); the reverse being true for crystal yield.

4. Discussion

The purification data, taken together with the fact that crystals grow to at least an order of magnitude greater than the drops, indicates, contrary to expectations, that crystallisation does not occur primarily within the drops nor does particle growth occur as a result of drop coalescence. Were these the case the product would comprise aggregates of spheres with sizes similar to the emulsion drop size and purities would be equivalent to those obtained on a cooled surface. It would seem reasonable to assume that nucleation of m-CNB results from impacts between seeds and drops and that the resulting nuclei, being dispersed by Tensugex, move out into the aqueous phase. At constant crystallisation temperature the chemical potential of m-CNB will be higher in the liquid phase than in the crystalline phase. This means that crystals in contact with an aqueous phase, which is itself in equilibrium with melt, will experience a supersaturation and hence will grow. m-CNB will thus be transferred from the melt droplets to the crystals via the aqueous phase. This allows the growth of large single crystals and means that the growing

crystals are not in contact with impure melt. The development of the polar morphology results, presumably, from the fact that the p-CNB also has some solubility in water.

The consequences of this mechanism are profound since, as the m-CNB is transferred to growing crystals the drops will shrink and become richer in p-CNB. At any given temperature the final drop compositions should be given by the measured liquidus line in the phase diagram. From Fig. 2 this can be seen not to be the case. Hence, providing the p-CNB does not crystallise within the drops, there is no apparent reason why m-CNB crystals should not continue to grow as a pure phase and the drops become further enriched with p-CNB below the eutectic temperature, taking the liquid phase through the eutectic into the p-CNB side of the phase diagram. The data for the liquid and solid phases are consistent with the mechanistic prediction that in this emulsion system the eutectic can be broken as a result of kinetically controlled discrimination.

At larger drop diameters, high organic weight fractions and lower surfactant levels it seems most likely that loss in final crystal purity is largely associated with the state of aggregation of the crystals. For example the significant increase in purification above the critical micelle concentration of Tensugex (measured in this work to be around 0.02 wt%), suggests that the surfactant plays a key role not only in stabilising the emulsion but also in subsequent dispersion of the resulting crystals. Thus when there is too little surfactant, due either to operation below the cmc or to increases in the final mass fraction of crystals, the crystals are not dispersed but flocculate due to the hydrophobicity of their surfaces and trap uncrystallised drops thereby lowering the overall purity. The disadvantage of using high surfactant levels is the lower yields achieved due to the stabilisation of smaller drops which are reluctant to crystallise (Table 2). Larger drops tend to yield groups of crystals which again trap liquor and are impure; a similar picture is observed at high organic weight fractions.

A mechanism for crystallisation when either the organic weight fraction is high, or the surfactant weight fraction low (possibly at levels below the cmc) is suggested. That is, uncrystallised drops collide with already formed crystals and deposit their

contents to yield irregular morphologies in an uncontrolled growth process. At high organic weight fractions these collisions become statistically more probable leading to the observed increase in crystallisation rates. This can lead to polycrystalline aggregation and associated purity problems as discussed earlier. Control of final crystal size and morphology in this situation is clearly impossible.

5. Conclusion

We have shown that the crystallisation of emulsified impure *m*-chloronitrobenzene can form the basis of a purification process. For the case of *m*-chloronitrobenzene crystallising from mixtures with its para isomer, optimum purity and physical form of product crystals are obtained at low organic phase weight fractions and small (5 μm) drop diameters. In these systems the surfactant plays a dual role of both stabilising the emulsion and dispersing product crystals into the continuous (aqueous) phase.

Compared to traditional progressive freezing tech-

niques the emulsion process appears, uniquely, to offer excellent purification in a single stage. In addition, purification can be achieved below the thermodynamic eutectic temperature due to kinetic effects in which the crystallisation of impure drops is inhibited by their small size and the increasing levels of p-CNB.

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The low pressure required for molecular distillation is usually produced by coupling a "backing" pump (*e.g.*, a Cenco Hyvac or Edwards Speedivac pump) with *either* a multi-stage mercury diffusion pump in quartz or metal (these two are combined in certain pumps, *e.g.*, Cenco Hypervac 4) or an oil-vapour diffusion pump* (the oils used include amyl and butyl sebacate, amyl phthalate, di-2-ethylhexyl sebacate and phthalate, Apiezon B, Dow-Corning Silicone Nos. 702 and 703). The advantages of the latter are:—(i) the highly purified oils have vapour pressures of about one

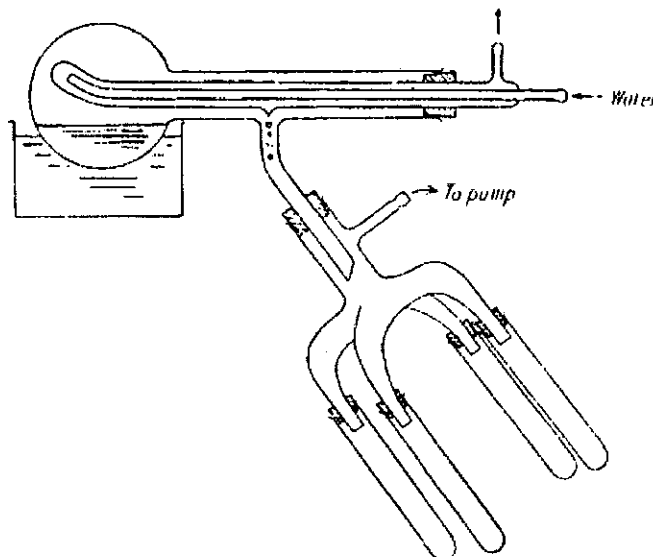


Fig. II, 26, 4.

hundredth of that of mercury and consequently produce lower pressures without the use of traps, and (ii) no contamination from mercury is possible. A McCleod gauge is generally utilised for measuring the low pressure.

The purification of solids by low pressure sublimation is described in Section II,45.

II,27. PURIFICATION OF SOLID ORGANIC COMPOUNDS BY CRYSTALLISATION

GENERAL CONSIDERATIONS

Solid organic compounds when isolated from organic reactions are seldom pure; they are usually contaminated with small amounts of other compounds ("impurities") which are produced along with the desired product. The purification of impure crystalline compounds is usually effected by crystallisation from a suitable solvent or mixture of solvents. Attention must, however, be drawn to the fact that direct crystallisation of a crude reaction product is not always advisable as certain impurities may retard the rate of crystallisation and, in some cases, may even prevent the formation of crystals entirely; furthermore, considerable loss of

* Supplied, for example, by the Scientific Glass Apparatus Co.

material may occur. It is therefore, desirable, if possible, to adopt other methods of preliminary purification (*e.g.*, steam distillation (Section II,40); distillation under diminished pressure (Section II,19); fractional distillation (Section II,15); extraction in a Soxhlet or equivalent apparatus (Section II,44)) before crystallisation.

The purification of solids by crystallisation is based upon differences in their solubility in a given solvent or mixture of solvents. In its simplest form, the crystallisation process consists of: (i) dissolving the impure substance in some suitable solvent at or near the boiling point, (ii) filtering the hot solution from particles of insoluble material and dust, (iii) allowing the hot solution to cool thus causing the dissolved substance to crystallise out, and (iv) separating the crystals from the supernatant solution (or mother liquor). The resulting solid, after drying, is tested for purity (usually by a melting point determination, Section II,10) and if found impure, it is again recrystallised from fresh solvent. The process is repeated until the pure compound is obtained; this generally means until the melting point is unchanged.

The theory underlying the removal of impurities by crystallisation may be understood from the following considerations. It is assumed that the impurities are present in comparatively small proportion—usually less than 5 per cent. of the whole. Let the pure substance be denoted by A and the impurities by B , and let the proportion of the latter be assumed to be 5 per cent. In most instances the solubilities of A (S_A) and of B (S_B) are different in a particular solvent: the influence of each compound upon the solubility of the other will be neglected. Two cases will arise for any particular solvent: (i) the impurity is more soluble than the compound which is being purified ($S_B > S_A$) and (ii) the impurity is less soluble than the compound ($S_B < S_A$). It is evident that in case (i) several recrystallisations will give a pure sample of A , and B will remain in the mother liquors. Case (ii) can be more clearly illustrated by a specific example. Let us assume that the solubility of A and B in a given solvent at the temperature of the laboratory (15°) are 10 g. and 3 g. per 100 ml. of solvent respectively. If 50 g. of the crude material (containing 47.5 g. of A and 2.5 g. of B) are dissolved in 100 ml. of the hot solvent and the solution allowed to cool to 15° , the mother liquor will contain 10 g. of A and 2.5 g. (*i.e.*, the whole) of B ; 37.5 g. of pure crystals of A will be obtained.

The most desirable characteristics of a solvent for recrystallisation are: (a) a high solvent power for the substance to be purified at elevated temperatures and a comparatively low solvent power at the laboratory temperature or below; (b) it should dissolve the impurities readily or to only a very small extent; (c) it should yield well-formed crystals of the purified compound; and (d) it must be capable of easy removal from the crystals of the purified compound, *i.e.*, possess a relatively low boiling point. It is assumed, of course, that the solvent does not react chemically with the substance to be purified. If two or more solvents appear to be equally suitable for the recrystallisation, the final selection will depend upon such factors as ease of manipulation, inflammability and cost.

The common solvents available for recrystallisation are collected in the Table II, 27.

TABLE II, 27. COMMON SOLVENTS FOR RECRYSTALLISATION

SOLVENT	B.P.	REMARKS
Water (distilled)	100°	To be used whenever suitable.
Diethyl ether	35°	Inflammable; avoid wherever possible.
Acetone	56°	Inflammable; should preferably be dried before use.
Chloroform	61°	Non-inflammable; vapour toxic.
Methyl alcohol	64·5°	Inflammable; poisonous.
Carbon tetrachloride	77°	Non-inflammable; vapour toxic.
Ethyl acetate	78°	Inflammable.
Methylated (industrial) spirit	77-82°	Inflammable.
Rectified spirit (95 % C_2H_5OH)	78°	Inflammable.
Ethyl alcohol (absolute) . .	78°	Inflammable.
Benzene	80°	Inflammable.
Light petroleum (petroleum ether)	40-60°	Inflammable.*
Acetic acid (glacial)	118°	Not very inflammable; pungent vapours.

The use of ether as a solvent for recrystallisation should be avoided wherever possible, partly owing to its great inflammability and partly owing to its tendency to creep up the walls of the containing vessel, thus depositing solid matter by complete evaporation instead of preferential crystallisation. Carbon disulphide, b.p. 46°, should never be used if an alternative solvent can be found; it has a dangerously low flash point and forms very explosive mixtures with air.

Less commonly used solvents include methyl ethyl ketone, b.p. 80°; ethylene chloride, b.p. 84°; dioxan (diethylene dioxide), b.p. 101° (vapours are toxic); toluene, b.p. 110°; pyridine, b.p. 115·5°; chlorobenzene, b.p. 132°; cellosolve (ethylene glycol monoethyl ether), b.p. 134·5°; di-*n*-butyl ether, b.p. 141°; *s*-tetrachloroethane, b.p. 147°; nitrobenzene, b.p. 209·5°; and ethyl benzoate, b.p. 213°.

The choice of solvent cannot usually be made on the basis of theoretical considerations alone (see below), but must be experimentally determined, if no information is already available. About 0·1 g. of the powdered substance is placed in a small test-tube (75 × 11 or 110 × 12 mm.) and the solvent is added a drop at a time (best with a calibrated dropper, Fig. II, 27, 1) with continuous shaking of the test-tube. After about 1 ml. of the solvent has been added, the mixture is heated to boiling, due precautions being taken if the solvent is inflammable. If the sample dissolves easily in 1 ml. of cold solvent or upon gentle warming, the solvent is unsuitable. If all the solid does not dissolve, more solvent is added in 0·5 ml. portions, and again heated to boiling after each addition. If 3 ml. of solvent is added and the substance



Fig. II, 27, 1.

* Other fractions available are b.p. 60-80°, 80-100°, and 100-120°: when the boiling point exceeds 120°, it is usually called "ligroin."

does not dissolve on heating, the substance is regarded as sparingly soluble in that solvent, and another solvent should be sought. If the compound dissolves (or almost completely dissolves *) in the hot solvent, the tube is cooled to determine whether crystallisation occurs. If crystallisation does not take place rapidly, this may be due to the absence of suitable nuclei for crystal growth. The tube should be scratched below the surface of the solution with a glass rod; the fine scratches on the walls (and the minute fragments of glass produced) may serve as excellent nuclei for crystal growth. If crystals do not separate, even after scratching for several minutes and cooling in an ice-salt mixture, the solvent is rejected. If crystals separate, the amount of these should be noted. The process may be repeated with other possible solvents, using a fresh test-tube for each experiment, until the best solvent is found; the approximate proportions of the solute and solvent giving the most satisfactory results should be recorded.

If the substance is found to be far too soluble in one solvent and much too insoluble in another solvent to allow of satisfactory recrystallisation, mixed solvents or "solvent pairs" may frequently be used with excellent results. The two solvents must, of course, be completely miscible. Recrystallisation from mixed solvents is carried out near the boiling point of the solvent. The compound is dissolved in the solvent in which it is very soluble, and the hot solvent, in which the substance is only sparingly soluble, is added cautiously until a slight turbidity is produced. The turbidity is then *just* cleared by the addition of a small quantity of the first solvent and the mixture is allowed to cool to room temperature; crystals will separate. Pairs of liquids which may be used include: alcohol and water; alcohol and benzene; benzene and petroleum ether; acetone and petroleum ether; glacial acetic acid and water.

The following rough generalisations may assist the student in the selection of a solvent for recrystallisation, but it must be clearly understood that numerous exceptions are known (for a more detailed discussion, see Section XI,4):

1. A substance is likely to be most soluble in a solvent to which it is most closely related in chemical and physical characteristics.
2. In ascending a homologous series, the solubilities of the members tend to become more and more like that of the hydrocarbon from which they may be regarded as being derived.
3. A polar substance is more soluble in polar solvents and less soluble in non-polar solvents.

II,28. EXPERIMENTAL DETAILS FOR RECRYSTALLISATION

It is assumed that the best solvent and the approximate proportions of solute and solvent have been determined by preliminary tests as described in the previous Section or have been obtained from reference

* If the crude substance contains an insoluble impurity, difficulty may be experienced at a later stage in estimating how much solute has crystallised from the cold solution. The hot solution should therefore be filtered into another tube through a *very small* fluted filter paper contained in a small short-stemmed funnel. The solution must always be clear before cooling is attempted.

books containing solubility data.* The solid substance is placed either in a small bolt-head flask or conical flask and slightly less than the required quantity of solvent is added together with a few fragments of porous porcelain or, better, a boiling tube (Fig. I, 3, 1); a reflux condenser is then fitted to the flask (Fig. II, 13, 7). If the solvent is not inflammable, toxic or expensive, the reflux condenser is not essential and may be replaced by a funnel with a short stem. The mixture is boiled and more solvent is added down the condenser (or directly into the flask if a condenser is not employed) until a clear solution, apart from insoluble impurities,† is produced. If the boiling point of the solvent is below 80°, a water bath (Fig. II, 5, 1) or steam bath is satisfactory; for solvents of higher boiling point an air bath (Fig. II, 5, 3), electric hot plate, or asbestos-centred wire gauze should be used.

Filtration of the hot solution. The boiling or hot solution must be rapidly filtered before undue cooling has occurred. (If an inflammable solvent has been used, all flames in the vicinity must be extinguished.) This is usually done through a fluted filter paper (for preparation, see Section II, 29) supported in a relatively large funnel with a short wide stem: separation of crystals in and clogging of the stem is thus reduced to a minimum. It is often advantageous to warm the funnel in the steam oven before filtration is started. The funnel is supported in a conical flask of sufficient size to hold all the solution; alternatively, the funnel may be clamped or supported in a stand and the filtrate collected in a beaker, but the use of a conical flask is preferable. If the operation has been successfully carried out, very little material will crystallise on the filter: any solid that does separate must be scraped back into the first flask, redissolved and refiltered. The filtered solution is covered with a watch or clock glass, and then set aside to cool undisturbed. If large crystals are desired, any solid which may have separated from the filtered solution should be redissolved by warming (a reflux condenser must be used for an inflammable solvent), the flask wrapped in a towel or cloth, and allowed to cool slowly. If small crystals are required, the hot saturated solution should be stirred vigorously and cooled rapidly in a bath of cold water or of ice.

If crystallisation commences as soon as the solvent cools or if large quantities of hot solution are to be filtered, the funnel (and fluted filter paper) should be warmed externally during the filtration (hot water funnel). Three types of hot water funnel are illustrated in Fig. II, 1, 6; no flames should be present whilst inflammable solvents are being filtered through the funnel of Fig. II, 1, 6, a. Alternatively, the funnel may be surrounded by an electric heating mantle (see Section II, 57); the heat input may be controlled by a variable transformer. When dealing with considerable volumes of aqueous or other solutions which do not deposit crystals rapidly on cooling, a Buchner funnel may be used for filtration (see detailed account in Section II, 1 and Fig. II 1, 7, c). The filter paper

* For example, Lange, *Handbook of Chemistry*, Ninth Edition (1956) (Handbook Publishers, Sandusky, Ohio); Seidell, *Solubilities of Inorganic and Organic Substances*, Third Edition (1941-1952) (Van Nostrand).

† The undissolved material will be readily recognised if preliminary solubility tests have been made (Section II, 27).

should be of close-grained texture and should be wetted with the solvent before suction is applied ; the solution may then be poured on to the filter.

The experimental details for recrystallisation from mixed solvents (or solvent pairs) will be evident from the account already given ; the best proportions of the two solvents are determined by preliminary small-scale experiments.

II,29. PREPARATION OF A FLUTED FILTER PAPER

The filter paper is first folded in half and again in quarters, and opened up as shown in Fig. II, 29, 1, a. The edge 2,1 is then folded on to 2,4 and edge 2,3 on to 2,4, producing, when the paper is opened, new folds at 2,5 and 2,6. The folding is continued, 2,1 to 2,6 and 2,3 to 2,5,

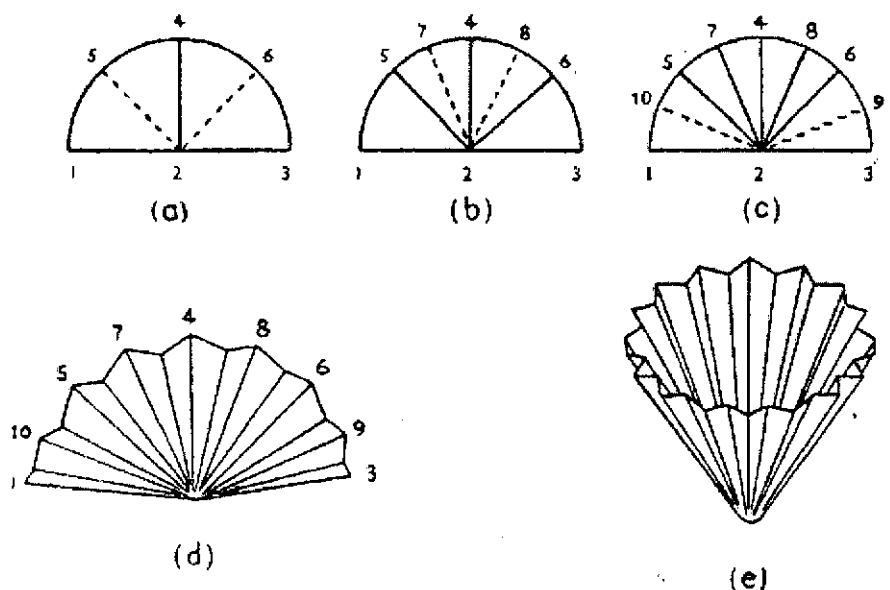


Fig. II, 29, 1.

thus producing folds at 2,7 and 2,8 respectively (Fig. II, 29, 1, b) ; further 2,3 to 2,6 giving 2,9, and 2,1 to 2,5 giving 2,10 (Fig. II, 29, 1, c). The final operation consists in making a fold in each of the eight segments—between 2,3 and 2,9, between 2,9 and 2,6, etc.—in a direction *opposite* to the first series of folds, i.e., the folds are made outwards instead of inwards as at first. The result is a fan arrangement (Fig. II, 29, 1, d), and upon opening, the fluted filter paper (Fig. II, 29, 1, e) is obtained.

II,30. REMOVAL OF TRACES OF COLOURING MATTER AND RESINOUS PRODUCTS USE OF DECOLOURISING CARBON

The crude product of an organic reaction may contain a coloured impurity. Upon recrystallisation, this impurity dissolves in the boiling solvent and is partly adsorbed by the crystals as they separate upon

cooling, yielding a coloured product. Sometimes the solution is slightly turbid owing to the presence of a little resinous matter or a very fine suspension of an insoluble impurity, which cannot always be removed by simple filtration. These impurities can be removed by boiling the substance in solution with a little decolourising charcoal for 5-10 minutes, and then filtering the solution while hot as described in Section II,28. The decolourising charcoal adsorbs the coloured impurity and holds back resinous, finely-divided matter, and the filtrate is usually free from extraneous colour, and therefore deposits pure crystals. The decolourisation takes place most readily in aqueous solution, but can be performed in almost any organic solvent; the process is least effective in hydrocarbon solvents. It must be pointed out that boiling in a solvent with decolourising carbon is not always the most effective method of removing the colour: if boiling is only partially effective, it is often worth while to pass the cold solution of the substance (preferably in an organic solvent such as ether) through a small amount of decolourising carbon supported on a wad of cotton wool in the stem of a funnel—this is effectively a chromatographic procedure.

An excessive quantity of decolourising agent must be avoided, since it may also adsorb some of the compound which is being purified. The exact quantity to be added will depend upon the amount of impurities present; for most purposes 1-2 per cent. by weight of the crude solid will be found satisfactory. If this quantity is insufficient, the operation should be repeated with a further 1-2 per cent. of fresh decolourising charcoal. Sometimes a little charcoal passes through the close-grained filter paper: the addition, before filtration, of a little asbestos fibre, filter paper pulp, high grade infusorial or diatomaceous earth will give a clear filtrate. Attention is directed to the fact that the decolourising charcoal should not be added to a superheated solution as the latter may foam excessively and boil over.

The most widely known form of decolourising carbon is animal charcoal (also known as bone black or bone charcoal); it is the least expensive, but by no means the best. It has limited adsorptive power, and contains a large proportion of calcium phosphate and other calcium salts; it should not be used with acidic solutions, particularly if the desired compound is to be subsequently obtained by a process of neutralisation. This difficulty may be overcome, and all risk of the introduction of impurities into the hot solution avoided, by boiling the commercial animal charcoal with dilute hydrochloric acid (1 : 1) for 2-3 hours. The mixture is then diluted with hot distilled water, filtered through a fine-grained filter paper supported on a Buchner funnel, and washed repeatedly with boiling distilled water until the filtrate is no longer acid. It is then well drained, and dried in an evaporating basin (or casserole) over an electric hot plate or a sand bath. Acid-washed decolourising charcoal is also available commercially.

On the whole it is better to employ the activated decolourising charcoal prepared from wood. Excellent decolourising carbons are marketed under the trade names "*Norit*"* (from birch wood), "*Darco*"* and "*Nuchar*."*

* Obtainable, for example, from Eastman Kodak Company.

II.31. DIFFICULTIES ENCOUNTERED IN RECRYSTALLISATION

The separation of a second liquid phase, commonly known as an "oil," instead of the expected crystalline solid, sometimes occurs during recrystallisation. The oil often solidifies on standing, although at times a considerable period may elapse before crystallisation occurs. The resulting crystals will probably occlude some of the mother liquor, and the purity will therefore not be high. If the substance has a low melting point, it must not be assumed that this apparently abnormal behaviour is due to the presence of impurities; it is probably an example of a system in which the solid phases consist of the pure components and the components are only partially miscible in the liquid state (see Section I,18). The separation of the oil may be avoided by diluting the solution considerably, but this will lead to large losses. It is probably best to re-heat the mixture until a clear solution is obtained, and allow it to cool spontaneously; immediately the oil commences to separate, the mixture is vigorously stirred so that the oil is well dispersed in the solution. Eventually, crystals will separate and these will grow in the bulk of the solution and not in a pool of oil, so that occlusion of the mother liquor is considerably reduced. When all the oil has disappeared, stirring may be stopped and the crystals allowed to accumulate. Sometimes the addition of a minute quantity of the crude compound in order to "seed" the solution may facilitate the initial crystallisation.

Occasionally substances form supersaturated solutions from which the first crystals separate with difficulty; this is sometimes caused by the presence of a little tar or viscous substance acting as a protective colloid. The following methods should be tried in order to induce crystallisation:—

1. By scratching the inside of the vessel with a glass rod. The effect is attributed to the breaking off of small particles of glass which may act as crystal nuclei, or to the roughening of the surface, which facilitates more rapid orientation of the crystals on the surface.

2. By inoculating ("seeding") the solution with some of the solid material or with isomorphous crystals, crystallisation frequently commences and continues until equilibrium is reached. The "seed crystals" may be obtained by cooling a very thin film of liquid to a low temperature. Several drops of the solution are placed in a test-tube or beaker and spread into a thin film by rotating the container; the latter is then cooled in a mixture of ice and salt or in some other suitable freezing mixture. A better procedure, which avoids the necessity of subsequently scraping the surface to remove the "seed crystals" and the attendant melting if the compound is impure or of low melting point, is to moisten a small glass bead with the supersaturated solution, place it in a test-tube, cool the latter in a freezing mixture and thus form crystals on the surface of the bead. The glass bead can then be rolled out of the tube into the vessel containing the main bulk of the solution.

3. By cooling the solution in a freezing mixture (ice and salt, ice and calcium chloride, or solid carbon dioxide and ether). It must be borne in mind that the rate of crystal formation is inversely proportional to the temperature; cooling to very low temperatures may render the mass

very viscous and thus considerably hinder crystallisation. In the latter case, the mixture should be allowed to warm slowly so that it may be given the opportunity to form crystals if it passes through an optimum temperature region for crystal formation. Once minute crystals have been formed, it is very probable that their size will be increased by keeping the mixture at a somewhat higher temperature.

4. By adding a few lumps of solid carbon dioxide; this produces a number of cold spots here and there, and assists the formation of crystals.

5. If all the above methods fail, the solution should be left in an ice chest (or a refrigerator) for a prolonged period. The exercise of considerable patience is sometimes necessary so as to give the solution every opportunity to crystallise.

The product of a chemical reaction, isolated by solvent extraction and subsequent removal of the solvent, which should normally be crystalline, is sometimes an oil, due to the presence of impurities. It is usually advisable to attempt to induce the oil to crystallise before purifying it by recrystallisation. Methods 1 and 2 (previous paragraph) may be applied; method 2 cannot always be used because of the difficulty of securing the necessary seed crystals, but should these be available, successful results will usually be obtained. Another procedure is to add a small quantity of an organic solvent in which the compound is sparingly soluble or insoluble, and then to rub with a stirring rod or grind in a mortar until crystals appear; it may be necessary to continue the rubbing for an hour before signs of solidification are apparent. Another useful expedient is to leave the oil in a vacuum desiccator over silica gel or some other drying agent. If all the above methods fail to induce crystallisation, direct recrystallisation may be attempted: the solution should be boiled with decolourising carbon as this may remove some of the impurities responsible for the difficulty of crystal formation. Occasionally, conversion into a simple crystalline derivative is applicable; subsequent regeneration of the original compound will usually yield a pure, crystalline solid.

II,32.

FILTRATION WITH SUCTION

The technique of the filtration of hot solutions has already been described in Section II,28. The filtration of cold solutions will now be considered; this operation is usually carried out when it is desired to separate a crystalline solid from the mother liquor in which it is suspended. When substantial quantities of a solid are to be handled, a Buchner funnel of convenient size is employed. The ordinary Buchner funnel (Fig. II, 1, 7, a) consists of a cylindrical porcelain funnel carrying a fixed, flat, perforated porcelain plate. It is fitted by means of a rubber stopper or a good cork into the neck of a thick-walled filtering flask (also termed filter flask, Buchner flask or suction flask) (Fig. II, 1, 7, c), which is connected by means of thick-walled rubber tubing (rubber "pressure" tubing) to a similar flask or safety bottle, and the latter is attached by rubber "pressure" tubing to a filter pump; the safety bottle or trap is essential since a sudden fall in water pressure may result in the water "sucking back." The use of suction renders rapid filtration possible