

ture at an appreciable rate, and when prepared in hexane it may come out of solution at the wrong moment especially at concentrations greater than 1M. Substitution by benzene or toluene can correct that, but often there are good reasons for not having an aromatic solvent present. However, there is a way of making a reasonably stable solution (ca 1.5M) in a cyclohexane-tetrahydrofuran mixture, directly from lithium metal with isoprene as hydrogen acceptor (the resulting 2-methylpropene rarely interferes afterwards):

In a 500 ml three-necked flask attached via drying tube to the multiple inert gas trap (see Chapter 4, Fig. 5) and containing a magnetic stirring bar is placed 110 ml of cyclohexane, 10 ml of which is then distilled out in an inert gas stream to ensure dryness of the remainder. After cooling to room temperature there are added, in order, dry diisopropylamine (63 ml), dry tetrahydrofuran (35 ml), freshly cut lithium (3.1 g, excess), isoprene (freshly distilled, 21 ml) and the razor blade shown in Fig. 2. The whole is stirred at $20 \pm 2^\circ\text{C}$ (occasional cooling may be needed) for at least 12 h (if left overnight the flask should be left in an insulated bath containing plenty of ice). The resulting solution (some lithium must be left over) is transferred by inert gas pressure (see Fig. 1) into 50 ml storage bottles which are tightly sealed with Parafilm and kept in the refrigerator until needed. Once a bottle has been opened, even with inert gas introduction, it will deteriorate rapidly. The exact content can be determined by the method of Watson and Eastham¹⁰³ (see below) using 2,2'-biquinolinyll as indicator.

Other Metal Dialkylamides

Another generally useful reagent based on lithium is the hexamethyldisilylazide, usually prepared from butyllithium and the corresponding amine. Presumably a stock solution of this can also be made directly from lithium metal as described above, although in lower concentration. One advantage of this base

seems to lie in its lower nucleophilicity and that of the amine liberated (as well as rapid cleavage of the latter on aqueous work-up). It is often stated to be more selective than lithium diisopropylamide, but probably the main reason for that is that it is significantly less basic by several orders of magnitude.¹⁰¹ It has been suggested that bases of intermediate strength could be prepared from *N*-silylated primary amines.¹⁰²

Other such bases prepared from, e.g. dicyclohexyl, or *tert*-butylcyclohexyl- or isopropylcyclohexylamine or from 2,2,6,6-tetramethylpiperidine (for details see ref. 8) have been used where they have specific advantages; here the higher molecular weight amine liberated may complicate working-up.

A base of this type distinguished by exceptional stability over long periods (more than 2 years) at room temperature is sodium hexamethyldisilylazide, which can be prepared in toluene from sodium hydride as follows:

Freshly distilled hexamethyldisilylazane is added to an excess (15–20%) of hexane-washed sodium hydride suspension in dry toluene in an amount calculated to lead to a 0.7–0.9M solution; the suspension is heated under reflux for at least 24 h. After cooling, the excess of sodium hydride is allowed to settle and the supernatant solution transferred to bottles which are tightly sealed and kept at room temperature (in winter some material may crystallise out but will redissolve on gentle warming).

Titration of C–Li and N–Li Bases

The methods suggested in recent years fall roughly into two categories: the first involves titration of the base against a weighed stoichiometric amount of a reagent, itself dissolved in a solvent whose dryness has to be assured, which forms a dianion the appearance of the intense colour of which indicates the end-point. The other utilises the formation of an intensely coloured complex between the base and a small amount of an indicator, the colour of which is discharged at the end-point by

titration with a standard solution of an acid or alcohol. The latter is, of course, much more convenient, particularly the method of Watson and Eastham,¹⁰³ where the indicator can be one of a number of heterocyclic compounds whose common feature is two nitrogen atoms in a 1,4-relationship. These form coloured charge-transfer complexes with many organometallics, and the choice between them (e.g. *o*-phenanthroline, 2,2'-dipyridyl, 2,2' diquinoliny) may depend on the base and on personal preferences as to colour. As titrant standard solutions of *sec*-butanol or menthol in toluene or xylene can be used. An advantage of this method is that it works also with amide bases and with Grignard reagents, but it gives best results when the solvent is at least in part hydrocarbon (which makes it easy to achieve dry conditions by azeotropeing). The indicator may also be used in a reaction mixture; here the amount of base needed until appearance of colour is an indication of the dryness of the solvent. This does not work so well with tetrahydrofuran, in which case a better indicator is the intense blue dianion colour formed with *N*-benzylbenzamide.¹⁰⁴

Alkoxide Bases

Solid sodium methoxide is a good base for many large-scale reactions, but the commercially available material should always be regarded with suspicion. It should be freely soluble in anhydrous methanol with no more than a trace of precipitate (sodium carbonate). Far too often it is still supplied in polyethylene containers, which are far more pervious to water vapour and carbon dioxide than is generally known. The same remarks apply to potassium *tert*-butoxide, with the additional problem that it is not easy to ascertain how much is unsolvated and how much the alcoholate. The only way to make sure is to sublime it in a high vacuum. Figure 3 shows a large test-tube adapted for this purpose; its diameter is just less than that of a Kugelrohr oven; the rubber stopper and stopcock have to fit precisely to assure the highest possible vacuum (0.05 mmHg or better) which will allow sublimation below 200 °C. After opening, best

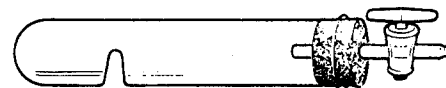


Fig. 3.

in a dry-box with the tube kept carefully horizontal, the material is carefully and rapidly scraped out using a sharp spatula with a bent tip into a rubber-stoppered bottle.

Sodium *tert*-amyl oxide is soluble in aromatic hydrocarbons such as toluene. The solution is easily prepared by heating under reflux for 12 h a known amount of the anhydrous alcohol in toluene with a 30% excess of sodium, which remains melted and reactive throughout. This must be done with strict exclusion of both moisture and oxygen, to which the solution is particularly sensitive. The subsequent transfer is best done into bottles of no more than 25 ml capacity unless a large amount is required immediately. Also, if the concentration is greater than ca 1.4 M it may crystallise out, and hence this reagent is best kept in a warm place (30–35 °C). The corresponding potassium alkoxide appears to be much more soluble^{105,106} (up to 2.1 M even under refrigeration); here benzene may be used since its boiling point is above the melting point of the metal.

Metal Hydrides

Sodium hydride, usually supplied oil-coated, presents few problems except that the effective real concentration is nearly always less than claimed. To be on the safe side, a weighed amount should be added to isopropanol followed by addition of water and titration with standard acid. Also, after prolonged standing, material at the top of the bottle tends to differ from that at the bottom and occasional vigorous mixing is recommended. Potassium hydride is much more difficult to handle because manufacturers have still not found a way to supply it in a form similar to sodium hydride. The material always settles out as a sludge in the oil whose specific gravity and other properties are never revealed. There seems to be no choice other than vigor-

ously shaking the suspension, immediately withdrawing it by volume, assuming a specific gravity of 0.90 in case of material claimed to be '20%', and then washing it through the pipette with hexane into the reaction flask (the pipette should be of polypropylene with the tip cut back to give an opening of 2 mm). However, to obtain more reliable results it is necessary to use a tared reaction flask with a stopcock, dry the introduced material after washings *in vacuo*, admit dry argon and weigh again.

Lithium hydride is generally available only as the unprotected solid whose effective content is both uncertain and difficult to determine except gasometrically. In practice, an excess of up to 50% is used which, because of its relative inertness, rarely causes problems.

Radical Anion Bases

Alkali metals react with polycyclic aromatic hydrocarbons, in particular naphthalene, in solvents such as tetrahydrofuran or dimethoxyethane to give deeply coloured solutions, which are stable at room temperature and which contain the radical anion of the hydrocarbon. Since this is one of the easiest ways to prepare an organometallic, and certainly the cheapest when considering sodium and naphthalene, the question has often been raised of whether such species could function as non-nucleophilic bases for proton abstraction pure and simple. The answer is 'yes, with reservations.' As a proton base the naphthalene radical anion has been estimated to have a pK value of ca 33, and as such it has served in the deprotonation of substrates such as ketones, aldehydes, nitriles and acetylenes and in the formation of dianions from carboxylic acids and acetylenic alcohols, i.e. all species more acidic than diarylalkanes in Table 1. The subject has been reviewed in some detail.¹⁰⁷ However, in many cases the yields (of products of subsequent reactions with electrophiles) have been far from impressive, and this is probably due, at least in part, to complications arising out of the electronic nature of the reagent. Also, in all such reactions there

is the practical problem of having to remove the polycyclic such as naphthalene, and its own transformation products such as dihydro products and dimers, usually by chromatography. One advantage of these reagents is that they are 'self-indicating' because of their intense colour.

More recently, the dual electronic nature of the species has been utilised in synthesis for the formation of carbanionic intermediates through reductive cleavage of carbon-sulphur bonds^{108,109} and carbon-halogen bonds.¹¹⁰ The latter has been shown to have particular value where formation of organolithium compounds directly from the halide and lithium metal leads to low yields, and a detailed examination has shown that instead of naphthalene the best results are obtained with 4,4'-di-*tert*-butyldiphenyl,¹¹⁰ a hydrocarbon which is now easily available as the product of a standard student exercise.¹¹¹ For solving the problem of subsequent working-up, the suggestion has been made of using 1-dimethylaminonaphthalene instead of naphthalene, making it possible to remove the spent reagent by acid extraction. However, the radical anion in this case has to be prepared and used below -40°C .¹¹²

AMINE BASES—MISCELLANEOUS USES

It would be difficult to discuss such bases in the same way as with Brønsted bases used specifically for *C*-deprotonation. They are weaker and have been used for direct *C*-deprotonation to a much lesser extent. Instead, they are used in a wide variety of reactions where specificity is more important than mere base strength. This can take the form of, e.g., specific interaction with the substrate (such as hydrogen bonding in elimination reactions) or specifically unstable and active intermediate formation (e.g. acylation).

Table 2, compiled for 15 important nitrogen bases, is intended to give some idea of the extent to which they have been used in 18 types of reactions of general importance. Since many of these are done on a large scale and with at least stoichio-

Table 2. Amine bases (amines, amidines, guanidines): Relative frequency of use in various reactions

Reaction type/ reagent	Amine ^a														
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
<i>O</i> -Acylation (e.g. by anhydride or halide)				+			# ^f	++			+	+ ^f	+		++
<i>O</i> -Alkylation (e.g. tritylation)						+++	+++ ^f								
<i>O</i> -Silylation				+		+++						+ ^b		++	+
<i>N</i> -Acylation (e.g. BOC formation)								+		+		++			+++
Dehydrohalogenation	++	+++	+	#	+++ ^c	+ ^c				+++					+++ ^c
Other β -eliminations			+					+	++	+	+++				+
Acid scavenger	+			+	+++ ^d	+			++	+	+++				+++

Amines (cost per gram-mol in parentheses):

- A: *s*-collidine (4.50)
 B: 1,5-diazabicyclo[4,3,0] non-5-ene, DBN (27)
 C: 1,4-diazabicyclo[2,2,2]octane, DABCO (8.40)
 D: 1,8-diazabicyclo[5,4,0]undec-7-ene, DBU (22)
 E: *N,N*-diethylaniline (1.60)
 F: diisopropylethylamine (12)
 G: 4-dimethylaminopyridine, DMAP (33)
 H: *N,N*-dimethylaniline (0.83)
 I: hexamethyldisilazane (12)
 J: *N*-methylmorpholine (2.5)
 K: pyridine (1.77)
 L: 4-pyrrolidinopyridine (458)
 M: 1,1,3,3-tetramethylguanidine (13)
 N: 2,2,6,6-tetramethylpiperidine (114)
 O: triethylamine (0.83)

Esterification (acid and halide or sulphate)	++			++		+++ ^f						+	+++ ⁱ		+
Ester cleavage (β -keto ester,															
malonate)			#			+									++
Macrolactonisation						+									++
Macrolactamisation						+									++
Michael or other conjugative addition				+	+								++		+
Reactive methylene condensation			+	+	++						++				++
Reactive methylene alkylation													+++		++
Reactive methylene acylation				+			+++ ^f								+
Dehydration with sulphonyl halide								+							+
Wittig reaction, formation of ylide															+
Peptide coupling			+										+++ ^e	+	+++ ^j

^a +, Used occasionally; ++, used frequently; +++, used very frequently; #, reagent of choice.

^b Causes aldol condensation at α -position of α,β -unsaturated ketones with aldehydes.

^c Advantages of high b.p.

^d Hydrochloride non-hygroscopic, easily filtered.

^e Used in ketene formation from α -haloacyl halides.

^f Active in catalytic amounts, for review see E. F. Scriven, *Chem. Soc. Rev.*, 12, 129 (1983).

^g Does not cause racemisation.

^h Selective reaction.

ⁱ Can catalyse formation even of isopropyl esters from isopropyl halides.

^j Hydrochloride insoluble; product isolated from filtrate.

metric amounts, Table 2 also contains data on their relative cost (which is approximate and in Swiss francs or German marks for convenience only), a factor often overlooked in a group of reagents where this factor can differ from one reagent to another by two orders of magnitude.

8

On Small-scale Distillation

FRACTIONAL DISTILLATION

When one considers the glassware encountered in most laboratories and offered by the great majority of glassware manufacturers, one is struck by the lack of suitable apparatus for fractional distillation of quantities of between 1 and 15 ml. This range is, of course, between that commonly dealt with by preparative gas chromatography and that encountered in the teaching laboratory.

For very accurate work there are spinning band columns, and micro and semimicro versions are commercially available. However, they are expensive and their repair is a task which even experienced glassblowers are reluctant to undertake. Most experienced workers solve this problem on an *ad hoc* basis by asking the glassblower to make up a suitable apparatus for a particular distillation at hand, after which it is usually relegated to a distant corner and its existence kept a dark secret.

The main problem in fractionation on this scale lies in loss of material, caused by (a) insufficient immersion of the stillpot, (b) too long a distillation path and flooding caused by too many bends and joints and resulting constriction, (c) excessive hold-up due to inappropriate column filling and (d) further loss of distillate on the way out caused by impeded outflow, unnecessary use of a condenser or use of one with an excessive internal surface.

Several years of experience in the author's laboratory has established the overall advantages of the type of distillation flask shown in Fig. 1. A set of three, with bulbs of 10, 25 and

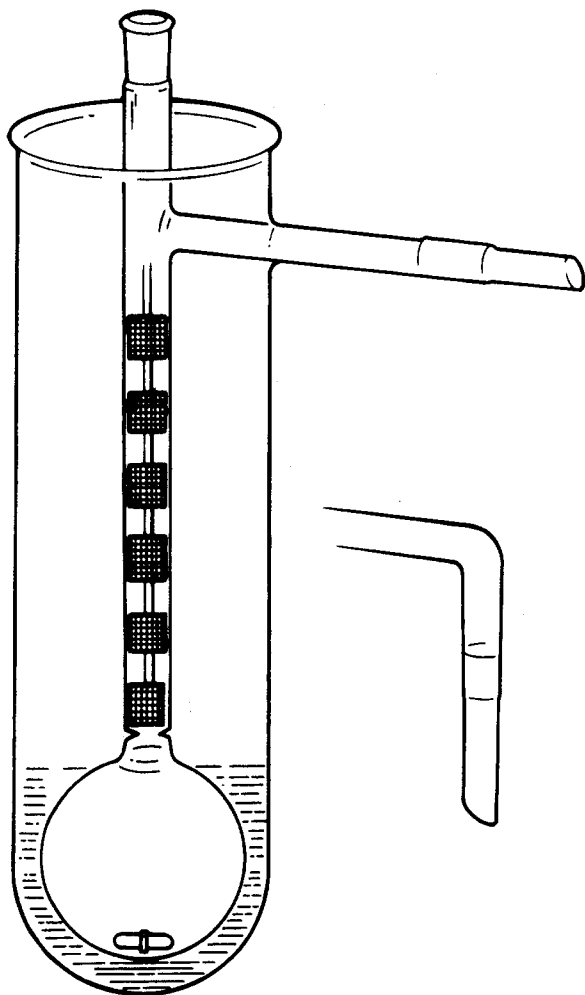


Fig. 1.

50 ml capacity and the other dimensions sized appropriately, should cover most amounts commonly encountered. The jacket into which the flask is fused (low enough so that magnetic stirring of contents is possible) serves two purposes: to protect the column from draughts, and to make it possible to add more heating medium up to the very top, in the case of very high-boiling materials. The outlet tube can be straight at the usual $60-75^\circ$ angle, or bent down again, finally parallel to the jacket in order to benefit from the two possibilities of connection to the fraction collector shown in Fig. 3. For the latter purpose it is necessary that the dimensions of the flask from the joint outwards be standard.

With these flasks the temperature gradient between that of the heating medium and the distillation temperature rarely exceeds 5°C , except of course with liquids of exceptionally high heats of vaporisation.

The column filling is of the twisted wire gauze type,¹¹³ which gives separations much superior to those with the usual Vigreux type of column. It may not be as good as a packed column, but in contrast to the latter the hold-up and consequent loss of material are very small. Above all, it can be made very easily from metal gauze (nickel-chrome or stainless steel) and a pair of identical pliers. A strip of gauze of length 1.5 times the length

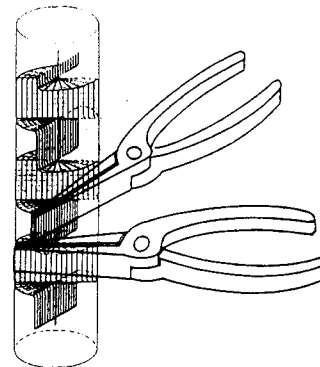


Fig. 2.

of the column and of width equal to the column's inner diameter plus two additional wire strands is cut, using scissors. The two additional strands are then stripped off and the resulting bare cross-strands bent down parallel to the strip. The latter should then slide *easily* into the column; if not, then one or two additional strands have to be removed. Portions of the strip (0.5–1 cm distant) are then held by the two pliers, one of which is then turned 90° to the other and the two are pressed together—this is repeated all along the strip. The procedure and the finished product are illustrated in Fig. 2. In practice, the latter rarely looks that good but that should not worry you unduly.

Such a filling is slowly attacked by, e.g., acyl and allyl halides, but it is so inexpensive and easy to make that this is hardly a deterrent.

The fraction collector shown in Fig. 3 is designed for both

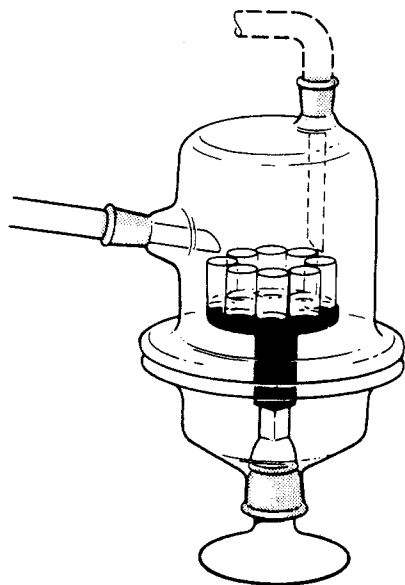


Fig. 3.

versions of the flask; in either case the vacant socket joint is used for vacuum take-off. As can be seen, it consists of two halves connected by a flange or O-ring joint. The former must, of course, be well greased and protected from heat. The lower half contains a ground-in turnkey on whose upper square end rests a shallow circular metal tray with rim, by means of a hollow square tube. The latter can be packed with internal spacers to permit variation in height. On the tray rimless vials of various sizes can be arranged circularly and kept in place either using a clock mainspring or by means of a suitably sized vial in the middle. Usually up to eight vials can be accommodated. The whole assembly is best supported by a support plate or movable platform ('lab-jack').

As for the absence of a condenser: very little cooling is usually needed on this scale and at the speed suitable for good fractionation. A piece of cotton-wool soaked in methanol or

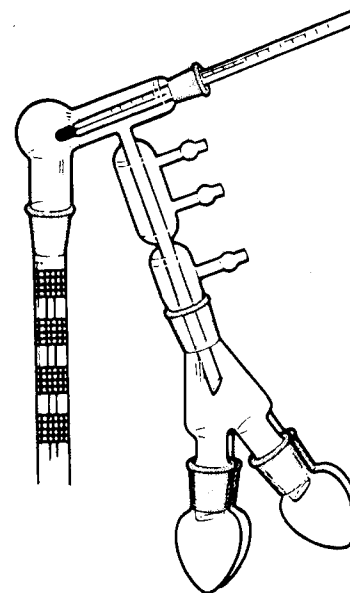


Fig. 4.

acetone placed on the outlet tube is usually sufficient; if not, then one can place a piece of dry-ice on top of that.

Other than that there is the possibility of modifying the top part of the flask shown in Fig. 1 in order to take advantage of one of the commercially available micro distillation heads with condenser and 'cow'-type fraction collector. The latter usually takes only four receivers, but with a very experienced glass-blower it can be modified to take more (see Fig. 4).

The proper way to fill the distillation flask is to take out the column filling, place it with the heating medium on a steam-bath, add the material for distillation, if necessary diluted with diethyl ether or dichloromethane, and then evaporate the transfer solvents in a partial vacuum. At the end of the distillation, while still hot, a suitable solvent can be added to dissolve the residue, which can then be withdrawn using a long capillary pipette. In this way, emptying out the heat medium each time can be avoided.

KUGELROHR DISTILLATION

The exceedingly useful and versatile Kugelrohr (for some inexplicable reason Kügelrohr to the Americans) oven should by now be in standard use even in undergraduate laboratories. It can be employed for distillation and sublimation of amounts ranging from 5 mg to over 30 g (see below). It is the fastest and most convenient way to purify preliminarily even the most messy looking product, provided of course that the desired part is thermally stable.

Bulbs connected by standard joints (Fig. 5) are now in general use. When using them it must be remembered that grease,

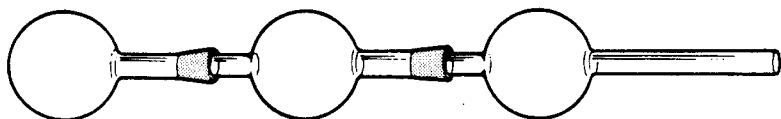


Fig. 5.

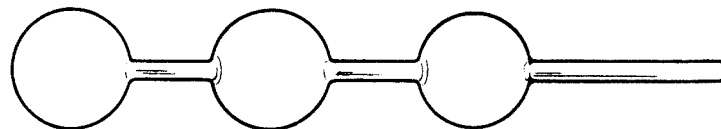


Fig. 6.

especially when hot and subjected to vacuum, may flow in and contaminate the product—hence only the upper wider part of the joint should be greased. If grease has to be avoided altogether, then the arrangement of connected bulbs (Fig. 6) should be employed. Incidentally, with both receiver arrangements some degree of fractionation can be achieved by first immersing the whole up to the last bulb in the oven, and withdrawing to the next in line as the temperature increases. When the amount to be distilled is large (more than one third of the distilling bulb's volume) it is essential to incline the whole arrangement at first and then bring it to level as distillation proceeds. Cooling is best done, once again, by a swab of cotton-wool soaked with methanol or acetone, but there is a device on the market (which your or your workshop's fertile imagination should not find difficult to reproduce) where the open end of a metal tube presses against the bulb from below, this tube containing pieces of ice, a perforated metal plate and a spring.

After the bulbs have been detached at the end of the distillation the contents, if liquid, can be withdrawn using a twice-bent capillary pipette (Fig. 7), or, if they have to be recrystallised, placed on an Erlenmeyer or round-bottomed flask with solvent on a steam-bath so that the contents are washed in by the rising solvent vapour and condensate (Fig. 8), with cooling by a piece of dry-ice at the point marked by an arrow.

Most commercial Kugelrohr ovens now have an arrangement that ensures oscillation or even rotation during distillation, so as to avoid bumping and splashing. This is useful to have, of course, if you can afford the extra amount that it will cost, but in most cases boiling stones or glass-wool and very carefully controlled heating will do just as well.

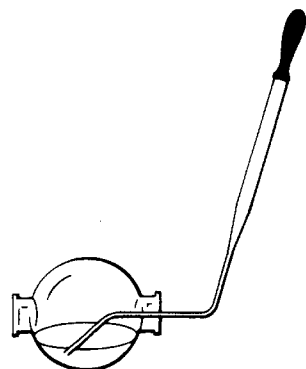


Fig. 7.

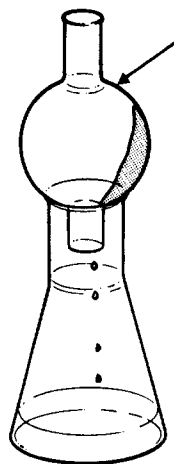


Fig. 8.

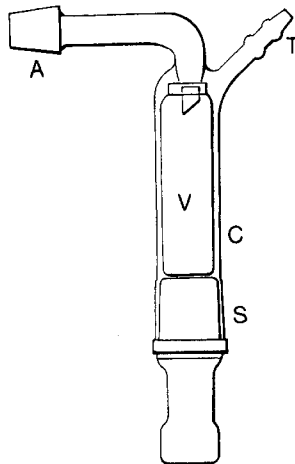


Fig. 9.

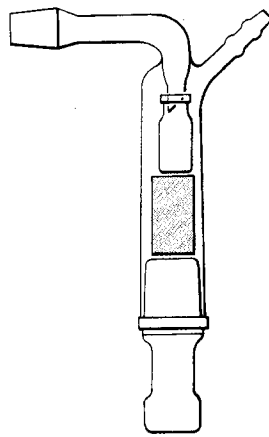


Fig. 10.

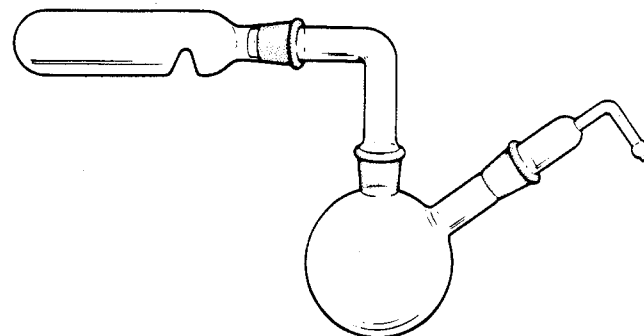


Fig. 11.

An arrangement which allows Kugelrohr distillation directly into a specimen vial, and has thus proved to be a great asset both in convenience and in saving money on flasks which are of an order of magnitude more expensive, is shown in Fig. 9. Here joint A leads to the flask in the Kugelrohr oven (not shown). S is a B24 stopper and the diameter of tube C is in accord. T is the vacuum outlet. The specimen vial V has in this case a capacity of 14 ml, but of course the arrangement can be used for smaller vials as shown in Fig. 10, using a piece of cork or rubber tubing cut to size as a spacer. The length of the inlet tube as shown suffices for methanol-soaked cotton-wool swab cooling if required; by careful use of a micro Bunsen burner the last traces of a viscous liquid can be transferred. Amounts of the order of 100–200 mg have thus been transferred with a recovery of 90–95%.

If the vacuum is applied via a Johnson multiple outlet trap (Chapter 4, Fig. 5), then in the case of air-sensitive distillates argon instead of air can be admitted after the distillation, and withdrawal and capping of the vial can be done in the inert gas stream. Naturally this device can be constructed in larger size (with a B34 stopper) and using a larger range of vial sizes.

When really large amounts have to be distilled by the Kugelrohr oven, arrangements such as that in Fig. 11 can be used. Here the size of the distilling vessel is limited only by the dimensions of the oven.

9

On Hydrogenation—The Cinderella of the Organic Experimentalist

It is difficult to understand the unpopularity of hydrogenation, other than the frequent absence of suitable apparatus. It is one of the cleanest synthetic operations, and sooner or later you will have to do one anyway, so why not plan to do it properly.

Except for very special cases, two basic set-ups are needed: one for doing hydrogenation at atmospheric pressure, for small amounts, in the 0.1–100 mmol range, and where hydrogen uptake needs to be measured accurately; and the other for medium-pressure (1–5 atm), for amounts generally ranging from 0.05 to 1 mol, although in principle it is possible to use the commercially available apparatus (see below) for either larger or smaller amounts.

THE ATMOSPHERIC PRESSURE SET-UP

A number of gas burettes, B, C, D (recommended: one of 25 ml, one of 100 ml and one of 500 ml capacity) are connected with each other, and on one side with the three-way stopcock A, A' [which are inlets for vacuum (water pump) and source of hydrogen] and on the other with items R, M and S as shown in

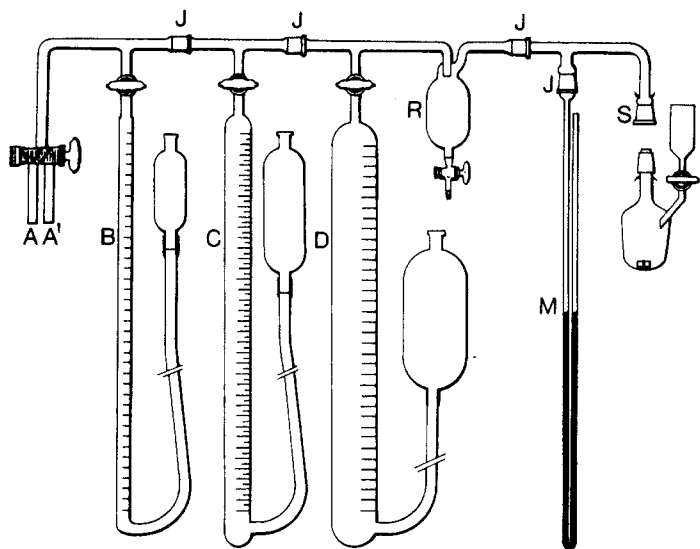


Fig. 1.

Fig. 1. The standard, necessarily high quality, joints J can be either the standard conical type making for tighter connections but also inflexibility, or the spherical type for greater flexibility but at the expense of more likely leaking. In either case they should be held together with suitable clamps (not shown). B, C and D each have their own reservoir of appropriate size attached; these should be filled with ca 2% copper sulphate solution, which will prevent algal growth over longer periods. R is a safety reservoir preventing the spill-over of burette liquid, M is a mercury-filled manometer and S is a female joint constituting the business end to which the hydrogenation flask is attached.

This is shown in greater detail in Fig. 2. It is of the shape advocated earlier for reaction flasks, to facilitate rapid and steady magnetic stirring, and is of one piece, connected to reservoir F via a stopcock (carefully greased). It should be noted that

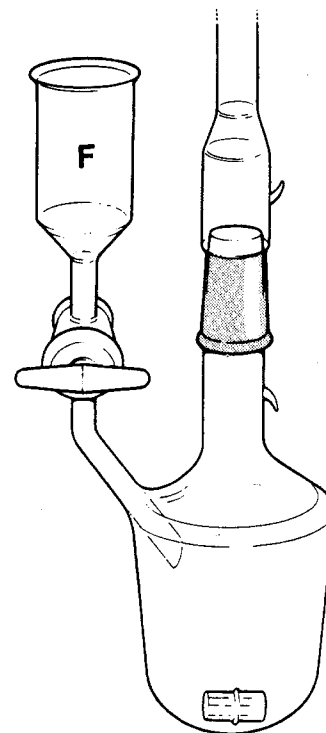


Fig. 2.

this apparatus, in contrast to similar ones in common use, completely avoids the use of rubber tubing, the usual source of leakage in a system where no leakage whatever should occur.

The detailed procedure is as follows. The hydrogenation flask containing the catalyst and just enough solvent to cover it is attached to S. With stopcocks leading to B, C and D closed, the system is evacuated via A, causing the mercury in M to rise. The stopcock of the chosen burette is then very carefully opened to raise the liquid just to stopcock level and thus expel all air, after which it is closed again. A is then closed, and hydrogen

admitted via A' until M shows the system to be at atmospheric pressure. This process of evacuation and hydrogen admission is repeated to make sure there is no air in the system. Finally, during hydrogen admission and with M showing slight excess pressure in the system, the stopcock of the chosen burette is opened and hydrogen allowed in to slightly more than the required volume, after which A and A' are closed. The system is now under hydrogen entirely, and magnetic stirring is started to prehydrogenate the catalyst.

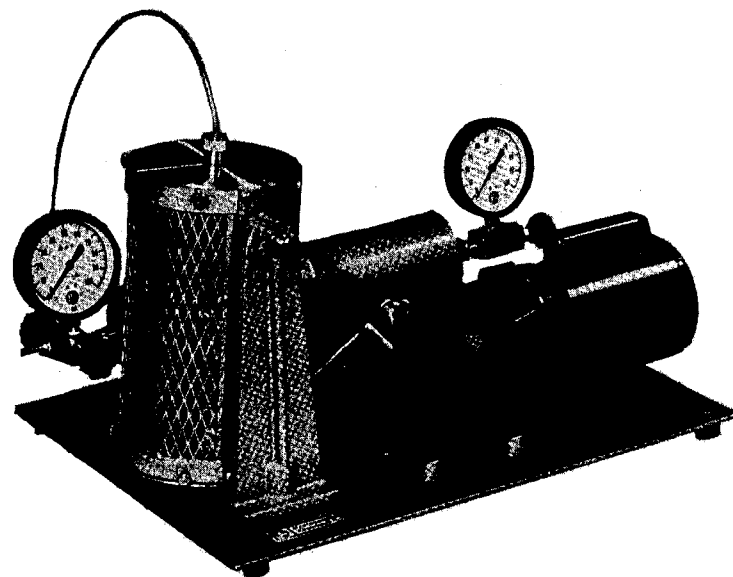
When this appears to be complete (cessation of uptake), stirring is stopped and the reservoir of the burette lowered to create a partial vacuum. The solution to be hydrogenated is placed in F and its stopcock is very carefully opened to run in the solution *except for the last drop* (so no air will get in). It is then washed in completely with small amounts of solvent using the same procedure. Stirring is then resumed for the hydrogenation proper.

When this is complete, all the hydrogen is pumped out *after* closing the burette stopcock, and then air is admitted, the flask disconnected, the suspension filtered and the solvent removed to isolate the product.

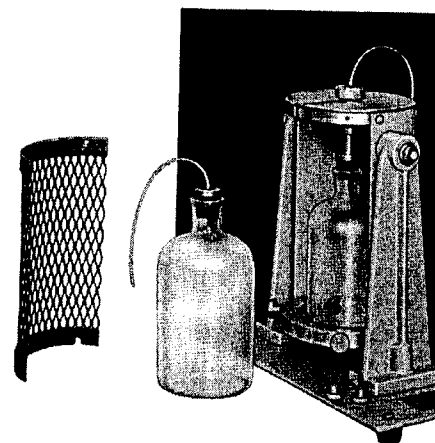
HYDROGENATION AT MEDIUM PRESSURE

With the advent of modern active catalysts, it is very rare that really high pressures are still needed for catalytic hydrogenation. The kind of apparatus that will allow doing so at up to 5 atm and, more importantly, for larger amounts, with little attention necessary during the process, is exemplified by that shown in Fig. 3(a), manufactured by Parr Instrument Co.¹¹⁴

A thick-walled glass bottle [Fig. 3(b)] inside a protective perforated metal cylinder is connected via a rubber stopcock (kept in place by a cross-piece and two thumbscrews), and by a flexible and pressure-tight plastic or metal tube to a main hydrogen reservoir (of 4 l capacity) which is filled via a stopcock to the right of Fig. 3(a). The glass bottle (of 500 or 200 ml capacity) can be shaken to and fro for agitation. There are two pressure



(a)



(b) Bottle clamp for above apparatus with guard screen removed.

Fig. 3. Reproduced by permission of the Parr Instrument Company.

gauges (still marked in lb/sq. in!), one showing the pressure inside the main reservoir and the other inside the glass bottle. It should be remembered that 1 atm equals ca 14.7 lb/sq. in, and that the reservoir and bottle should never be filled to more than ca 63 lb/sq. in. The procedure here is to clamp the bottle containing catalyst and substrate in solution (never tightening the screws to more than finger pressure) and evacuate the bottle only through a two-way tap (not shown); this allows entry of hydrogen from the reservoir in its second position. This evacuation-hydrogen admission cycle must be repeated at least twice. With large amounts the bottle is then shaken with the connection to the reservoir open. A pressure drop of ca 8.5 lb (right-hand gauge) corresponds to uptake of 0.1 mol of hydrogen. When hydrogenating smaller amounts it is preferable to use the smaller 200 ml bottle and shake with the reservoir connection closed. Uptake can then be calculated from the pressure drop on the bottle gauge using the expression

Pressure drop at NTP (lb/sq.in.)

$$= \frac{354}{\text{free volume}} \times \text{millimole H}_2 \text{ absorbed}$$

where the free volume is the volume of the bottle and connecting tube less the volume of the solution contained therein in millilitres. For very accurate work the uptake of catalyst and solvent must be determined by a blank experiment.

The most frequent source of leakage in this apparatus is where the flexible tube enters the glass bottle via a one-holed stopper. It is futile to use laboratory-made stoppers, and only those supplied with the apparatus should be used.

At the end of the hydrogenation the connection to the reservoir should be opened briefly so that the inrush of hydrogen will return solution which has found its way into the plastic connecting tube, otherwise it will end up in the stopcock block where material will crystallise out and cause a mess by blocking the system—cleaning that out is a special kind of aggravation. Vacuum is then applied to remove all the hydrogen; this should

be prolonged even with the solvent partly evaporating otherwise hydrogen will remain adsorbed and may cause an explosion when the system is opened to air.

SOME GENERAL REMARKS

At the beginning of this chapter it was said that hydrogenation is a clean reaction. That depends, of course, on how cleanly you start it, and that means solvent, catalyst and above all substrate. A melting point is not necessarily the criterion for the presence or absence of impurities which can act as catalyst poisons. If at all possible the substrate material should be redistilled or sublimed. If it results from a sequence which at any stage involved sulphur or selenium intermediates or reagents, it should be stirred in solution with silver powder or, better, passed through a column of an adsorbent containing ca 10% silver powder. When Lindlar catalyst is used (which is partly poisoned to start with), it has been found of great advantage to pass the substrate solution through a column of purified calcium carbonate.¹¹⁵ A hydrogenation which because of suspected poisoning takes days for completion either shows uptake because of leakage or because it is incomplete, or both. It is far better to stop, filter, use pure fresh catalyst or else purify the substrate!

The reactivity of a catalyst will decrease in proportion to how many times the bottle of commercially procured material has been opened, by how many people (whose personal habits cannot be followed) and over what period of time. In view of this, the range of platinum metal catalysts in the hydroxide form, whose preparation has been described by Pearlman,¹¹⁶ is highly recommended. They are non-pyrophoric and stable almost indefinitely. They must be pre-reduced immediately before use, which of course makes them always more active than the commercial product.

Catalyst recovery is a subject much like the weather—many people talk about it but few ever do anything about catalyst residues. Few if any books on catalytic hydrogenation ever bring up

the subject, probably in the knowledge that the amount of credit you will get from a supplier for returning them is nil unless industrial quantities are involved. Nonetheless, you should not throw away residues (probably bad for the environment too!), but recover them yourself when having nothing better to do. You may have to work out a procedure by yourself, though.

When carrying out a hydrogenation there is in most cases no need to have all the starting material in solution, since the product is generally much more soluble. Following this principle will often greatly increase the scale on which a hydrogenation can be conducted.

10

On Keeping It Clean

The fanatically tidy laboratory is more likely than not one where little work gets done, so if you are the type that gets things done you do not have to feel too guilty if there is a bit of a mess so long as it does not affect your results. That, of course, means fanatically clean equipment.

It should become an automatic habit to clean glassware preliminarily after use by dissolving out residues, before washing out with water-based detergents, none of which is capable of shifting most organic tars, whether this is attempted manually or in a machine. This is the best use to which to put recovered solvent mixtures, such as from a rotary evaporator.

Drying of glassware is preferably done in an oven, if there is room for all. If not, it has to be allowed to drain. The customary pegboard has disadvantages which are obvious with many types of item. A much better installation for the purpose is a horizontal drying rack (Fig. 1), which incorporates a framework of thin plastic-covered rods forming square or rectangular openings of various sizes. Here there is no contact with the inside of the vessel, and this is suitable not only for flasks but also for funnels, dishes and flat objects.

Although it is supposed to show up better in photographs when dirty, the necessity for clean glassware, especially in small-scale work, is rarely questioned. But when it comes to porcelain ware, 'what the eye does not see, the heart does not grieve over'.

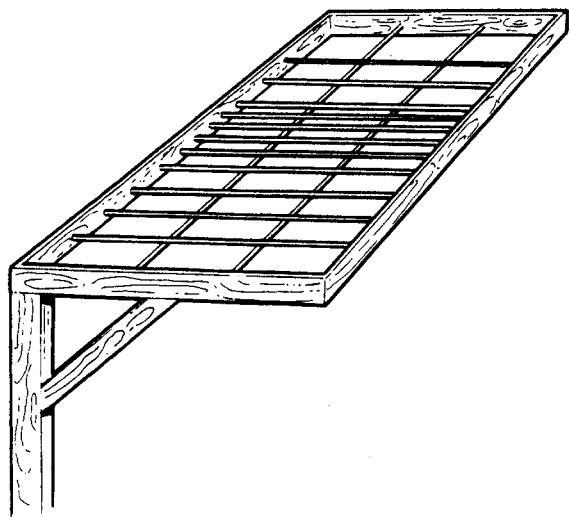


Fig. 1.

If at any time you feel like letting off steam by breaking something, choose a Buchner funnel—the result can be very instructive. One should make it a habit, automatically, to dissolve material and wash through a Hirsch or Buchner funnel into the vessel holding the mother liquor, and to make quite sure all such porcelain ware should be immersed in chromic acid at regular intervals.

A necessary but messy item in any laboratory is stopcock grease. The idea of dispensing it from a plastic syringe (without the needle), best of 10 ml size,¹¹⁷ is an excellent one, but only if this syringe is hung up in the way shown in Fig. 2, otherwise the weight of the plunger will slowly but surely deliver the grease where it is not wanted. For this one merely has to put two blobs of epoxy adhesive where shown, to hold the wiring in place.

And now to a more delicate observation. In many institutions the demand for cleaning tissue reaches alarming dimensions, at which point it becomes clear that it is being used for purposes best described as non-scientific. I now suggest a reasonable and

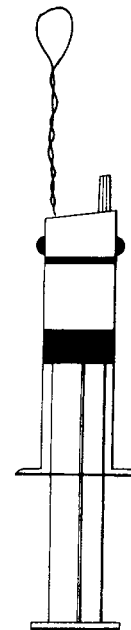


Fig. 2.

far more economic alternative: toilet paper. In principle it is exactly the same. You will soon get over the psychological block: and if the secretarial staff do not, so much the better.

Bottling Things Up

It is astonishing how often even experienced researchers, after devoting much thought and effort to the preparation of a pure product, become careless and thoughtless when it comes to bottling and storing it. The same still goes for manufacturers and suppliers, although with them there have been a good many improvements in the last few years.

With a few exceptions, which will be mentioned below, the glass bottle or vial is still the best receptacle. It does not necessarily have to be round—square and rectangular bottles are easy to come by and are better for storage where space is at a premium (e.g. in a refrigerator). Colour is another factor. Many organic compounds are sensitive to light and a lot of organic photochemical research has started by looking for those bottles on the shelf which show a colour change on the side facing the window—hence brown is preferable to colourless. However, the crucial problem is that of the type of closure to be used. The only completely satisfactory closure is that of the sealed tube and ampoule, but one can safely assume that this will be ruled out as impracticable in most cases.

GROUND-GLASS STOPPERS

These are definitely *out*, except for routinely used solvents on the laboratory bench where easy and rapid access is desirable,

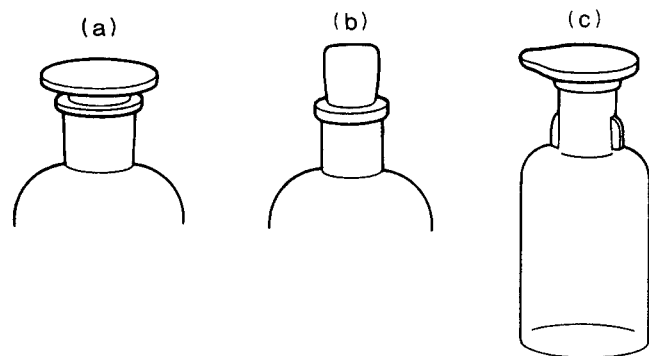


Fig. 1.

and for acids such as hydrochloric, sulphuric and acetic acid. In such cases, preference should be given to stoppers as shown in Fig. 1(a), which will keep the dust out, and not to the type shown in Fig. 1(b). The same consideration should apply to solvent dropping bottles (usually of 50–60 ml capacity), where the type shown in Fig. 1(c) is superior.

In almost all other cases glass-stoppered bottles should be given a wide berth. With volatile materials they offer little resistance to loss by evaporation and virtually none to entry of water vapour and air. With most inorganic solutions, especially if alkaline, evaporation or reaction with oxygen or carbon dioxide will cause 'freezing' of the stopper, which often cannot be removed. That means having to throw away the bottle, a two-fold problem: one a waste of money and effort invested, the other of disposal without causing immediate or potential harm to others.

All these considerations apply equally to the use of glass stoppers in reaction set-ups where there is another good reason: sudden development of pressure within a reaction system, a common enough occurrence, can convert a glass stopper into a dangerous projectile.

SCREW-CAP CLOSURES

These are still the best type on the whole, but much depends on what is inside the screw cap, i.e. the part that will be in direct contact with the substance inside. A mere cardboard or cork pad offers very little protection, neither from the outside in (water vapour, air) nor from the inside out (attack by contents on the plastic screw cap and beyond that on the label and on the surroundings). Many such pads have a plastic coating which will be found to dissolve in many organic liquids. An additional layer of aluminium foil offers little improvement.

Much better are screw caps with an inner cone of polyethylene or polypropylene [e.g. Fig. 2(a) and (b), with the latter preferred] or a cushion made of a Teflon-rubber laminate [Fig. 2(c)]. These are fully effective only with bottles whose rim is smooth and uniform and will press snugly under pressure of the screwed-home cap against the elastomer used. This type of closure is essential with contents such as solutions of organometallics, volatile amines (a particularly troublesome class of compounds), acyl halides and most Lewis acids such as boron trifluoride etherate, tin(IV) chloride, titanium tetrachloride (neat or in solution) and boron halides in solution. With other compounds, such as organoaluminium or organozinc compounds, even such screw caps are not satisfactory over longer periods, and such compounds should be left in the cylinders in which they are usually supplied and withdrawn only to the extent to which they are immediately used, or else for dilution by a suitable solvent—such solutions are usually less aggressive.

For storage over longer periods, additional sealing with Parafilm is recommended. To cut down on loss by evaporation

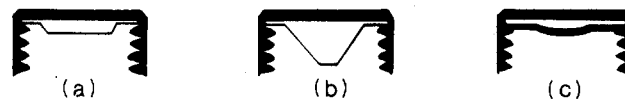


Fig. 2.

and spoilage even further, the bottles should be placed in a closed metal can, especially in a refrigerator where safety is an additional requirement.

PLASTIC (USUALLY POLYETHYLENE) BOTTLES

With these there is the advantage of no risk of breakage. They are satisfactory for most inorganic substances and solutions and in fact much superior to glass for concentrated alkaline solutions. Further, they are cheap. They can be used for organic substances provided that these are not affected by moisture, carbon dioxide or oxygen, to which polyethylene is much more permeable than generally realised. Another undesirable property of polyethylene to be on guard against over longer periods of time is deterioration by light and heat. It becomes brittle and cracks and large containers, e.g. containing distilled water, have been known to burst without prior warning.

There are some organic compounds which are known to suffer decomposition catalysed by impurities usually present on glass surfaces, such as alkyl chloroformates and solutions of diazomethane. Here storage in polyethylene bottles seems to be the only, although not completely satisfactory, solution.

BOTTLING AND STORAGE OF SMALL QUANTITIES—VIALS

These are where most of your products will end up, hence a good deal of thought should be devoted to this topic, depending on the properties of the stored substance.

In the author's experience, the best general type of vial for the storage of small amounts is the glass vial closed by a polyethylene stopper. The tall type [Fig. 3(a)] is to be preferred to the squat type [Fig. 3(b)], as there is less exposure of the stopper. The ribbed open-bottom type of stopper [Fig. 4(a)] provides

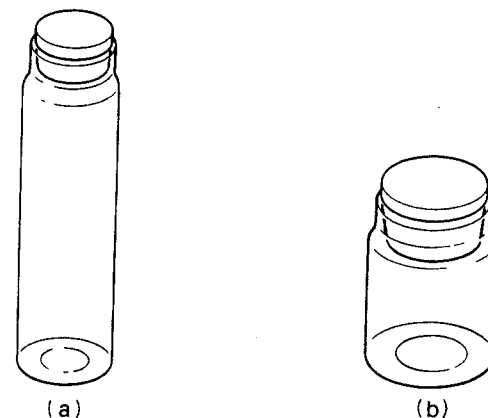


Fig. 3.



Fig. 4.

more reliable complete closure than the smooth 'solid' (actually hollow) type [Fig. 4(b)]. Such vials can be used for both solids and liquids, although in the latter case storage should be upright just to be on the safe side. Here too additional Parafilm sealing will augment protection.

As for screw-capped vials, the same problems as with screw-capped bottles are encountered, only more so because with these the cardboard or cork pad is still standard. For special cases it is possible to cut a suitable liner from silicone rubber sheeting using a very sharp cork borer—provided you can find one of just the right diameter.

Vials with closure of the 'snap-cap' type (Fig. 5) are con-



Fig. 5.

venient for easy access, but strictly only for innocuous solid materials and for purely temporary storage.

Now to vials with a septum closure for withdrawal by syringe, a reasonable variety of which are on the market. With all these there is just no getting around the fact that there is as yet no known elastomer which is impermeable and chemically and mechanically indifferent to all types of organic materials, and certainly not once it has been punctured. A Teflon liner does give extra protection, but that too only up to the point of first puncture. Hence the use of such vials should be restricted to cases where withdrawal by syringe only is envisaged, and then only for a limited time after first withdrawal; certainly not for long-time storage *per se*. Many such vials containing expensive volatile materials, closed by a septum held by a crimped metal closure, have been encountered which on arrival were completely empty—witness to the permeability of the type of material used.

Occasionally one encounters storage problems even on a small scale which need special treatment. A case in point is osmium tetroxide. This usually comes in 1 g sealed ampoules, but is now used mainly in catalytic amounts (10–100 mg) only. Hence, once such an ampoule had been opened the question arose of what to do with the rest of this highly volatile, very expensive and very toxic material. The solution lay in preparing a vial with a specially machined Teflon plug which alone prevented leakage (always easily shown up with this compound by the blackening of the surroundings).

METAL CANS

These are *not* suitable for storing your products. The fact that so many chemicals are now commercially supplied in cans, often of the snap-open beer can type, is for reasons of economy and safety in transit only. In fact, once such a can has been opened it is highly desirable to transfer the contents immediately to a glass container. The plastic lid usually supplied for subsequent closure should not be relied upon. This advice applies particularly to substances such as lithium aluminium hydride, sodium borohydride and hydrides of sodium, calcium and lithium. It does not apply to alkali metals supplied under mineral oil. For safety's sake these should remain in the screw-capped metal container in which they should usually arrive.

Naturally, none of these comments apply where the can is marked 'Bottle Inside' and where this is indeed found to be true!

LABELLING

For the synthetic organic chemist there are few aggravations to equal the bottle which has lost its label, or where the writing has become illegible through chemical attack or fading by light.

The most lasting inscription is that made by old-fashioned black ink. Electronic typewriting (based on carbon black) and the ordinary graphite pencil come a close second. Very few of the inks used in ball and felt pens are vapour- and light-fast. However, using the right type of ink is not enough. The label should be protected by a lacquer-type spray—the best is the type used for electrical insulation. Adhesive tape should never be used. It deteriorates in the course of time and the writing may diffuse into it and simply 'disappear'.

Special care should be taken with bottles kept in a freezer compartment, because the process of defrosting will detach almost any label. Hence, when the time comes, each bottle

should be taken out and allowed to defrost separately. An additional safeguard to forestall disaster is to tie an additional label on to the neck of the bottle. With vials, the small size of the label makes loss almost inevitable, and a good habit to acquire is to use a long label, somewhat longer than the vial's circumference, and allow the ends to stick together.

POLYETHYLENE PACKAGING

Many every-day goods and articles now come packaged sealed in polyethylene sheeting, and it should be pointed out that with the availability, at a reasonable price, of heat sealers (Fig. 6)

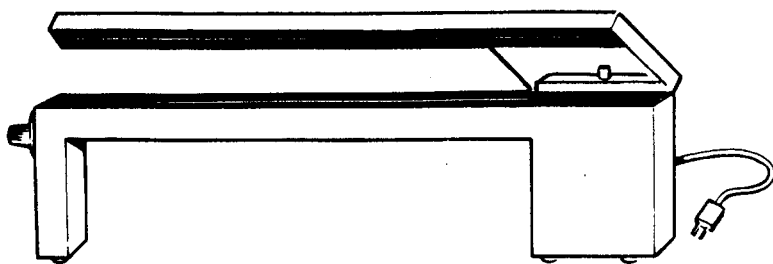


Fig. 6.

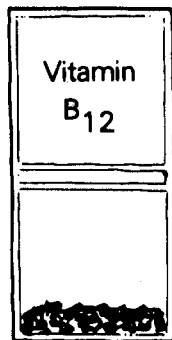


Fig. 7.

anybody can get into the act. Sealing of chemicals in polyethylene bags is a quick and convenient way of storage for limited periods, at any rate for reasonably stable compounds. Moreover, as far as solids are concerned, for dispatch of samples by mail this is by far the best way. Such samples should be sealed-in as illustrated in Fig. 7, with one compartment for the sample and one for the label, and the whole should be attached by adhesive tape, not stapled, to the letter.

One can think of a number of items in the laboratory which are used or used up intermittently and need to be protected from dust, excessive humidity or corrosion, such as preparative TLC plates, syringes, small lecture bottle gas cylinders, special gas regulators and special metal fittings. All such items can conveniently be protected by sealing in polyethylene enclosures.

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