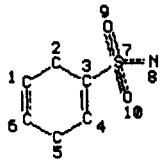
STN INTERNATIONAL



NODE ATTRIBUTES:
NSPEC IS RC AT 8

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 10

		******CONNECTIONS******			
NOD	SYM	NOD/BON	NOD/BON	NOD/BON	
1	C	2 RSE	6 RD		
2	C	3 RSE	1 RSE		
3	C	7 CSE	4 RDE	2 RSE	
4	C	5 RSE	3 RDE		
5	C	6 RSE	4 RSE		
6	C	1 RD	5 RSE		
7	S	10 CD	9 CD	8 CS	
		3 CSE			
8	N	7 CS			
9	O	7 CD			
10	O	7 CD			

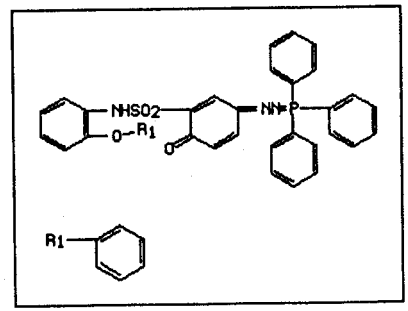
Fig. 2(a). Graphic input for a substructure search in the STN Registry File. Reproduced by permission of Chemical Abstracts Service, a division of the American Chemical Society.

a *R*ing *S*ingle *E*xact bond and to atom 6 by a *R*ing *D*ouble bond, etc.

A closer look at the connection table in Fig. 2(a), however, illustrates some of the problems that exist even with structure searching. There are two different kinds of double bonds in the figure: the one between atoms 3 and 4 is a localised double bond (specified upon entry as '*R*ing *D*ouble *E*xact', shown as such in the connection table in Fig. 2(a), drawn with two solid lines), while the double bond connecting atoms 1 and 6 is of a general type, including both localised (double line) and 'normalised' bonds (dotted line). Normalised bonds occur, for example, in benzene; by defining the double bond 1–6 as '*E*xact' like the other, you would automatically, but probably unknowingly and unintentionally, exclude all compounds with an anellated benzene ring! By defining it as normalised as in benzene, you would retrieve *only* such anellated compounds. The general

STN INTERNATIONAL

RN 105106-33-0
IN Phosphorane, [[4-oxo-3-[(o-phenoxyphenyl)sulfamoyl]-2,5-cyclohexadien-1-ylidene]h drazono]triphenyl- (6CI)
MF C36 H28 N3 O4 P S
SR CAOLD



REFERENCES IN FILE CAOLD (PRIOR TO 1967)
0 REFERENCES IN FILE CA (1967 TO DATE)

Fig. 2(b). Print-out of a compound found with the substructure in Fig. 2(a) in the STN Registry File. Reproduced by permission of Chemical Abstracts Service, a division of the American Chemical Society.

bond type is a good compromise here. A caveat is necessary: 'normalized' is not identical in meaning with the chemical term 'aromatic'; it is a formalised (computer-adequate!) definition including all even-membered rings with alternating single and double bonds—by that definition, cyclooctatetraene is 'normalised', but pyrrole is not! Another, similar bond differentiation is important in potentially 'tautomeric situations': tertiary sulphonamides (no hydrogen at the N) have localised, primary and secondary amide normalised bonds—the general bond type here again takes care of both cases. A carboxyl function has localised bonds in an ester, but normalised bonds in the free acid. You may not like these CAS bond conventions[29d] but for successful searches, you need to know and apply them correctly. There is yet another potential complication you must be aware of: the nitrogen in Fig. 2(a) bears a '*N*ode *SPEC*ification *R*ing or *C*hain'—every atom or bond not actually drawn in a ring is by

default assumed to be in a chain, and only there, unless you explicitly define it otherwise as we did in Fig. 2(a). Unless you take care of these definitions in the Registry File, you will miss relevant compounds.

One of the 134 compounds retrieved with the substructure in Fig. 2(a) from nine million in the Registry File (at that time) is shown in Fig. 2(b). This particular one is from the 'Pre-1965 Registration Project'[29b] mentioned above, because it has CAOLD in the *SouRce* field, and REFERENCES (only CAS abstract numbers) in that file, but none in the *CA* File. The other data fields in Fig. 2(b) contain the *R*egistry *N*umber, the CAS *I*ndex *N*ame, and the *M*olecular *F*ormula of this compound.

Substructure searching is particularly well suited to demonstrate the power of online searching. You can get fast and reliable answers to questions you would probably not have dreamt of asking ten years ago within the context of the printed sources. For example, suppose you are interested in all *coumarin glycosides* that have been isolated as natural products since 1980. For this it is necessary first to translate 'coumarin glycosides' into an acceptable substructure. This was done by creating four different substructures, each containing the coumarin skeleton as one structure fragment and a second 'pentose' or 'hexose' one in the cyclic or acyclic form, respectively—this is unconnected to allow attachment at different points in the coumarin ring (see Fig. 3). In order to retrieve all types including desoxy sugars, only the C-1 oxygen at the 6- and

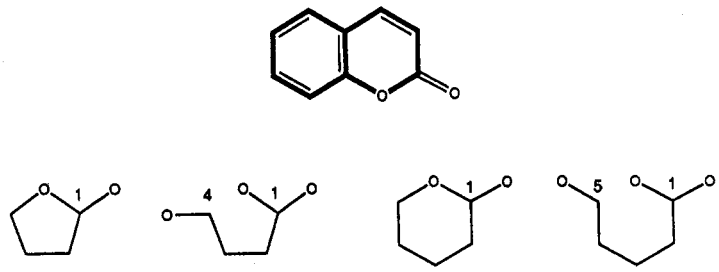


Fig. 3. Structure fragments used to retrieve 'coumarin glycosides'

5-ring fragment, respectively, and the C-1 and C-4(5) oxygens in the acyclic fragments were specified. A substructure search in the Registry File with these four substructures combined with the logical operator OR, limited to the period in question (this is done by restricting the search to a range of CAS Registry Numbers corresponding to the desired time period), gave 391 compounds. It was now necessary to identify all those isolated from natural sources. There are two ways of doing this. One is to print out all 169 literature references found for these compounds subsequently in the *CA* File and check them manually for 'isolation from natural sources'. This is reliable, but tedious. In this instance, you might not want to display them all on the screen while online (as we did in the earlier examples) and print them with a local printer attached to your terminal/personal computer, but enter a command to have them printed offline, i.e. with a laser printer at the computer facility, and then mailed to you. This 'offline printing' is usually a cheaper alternative for large amounts of output, particularly structures from a substructure search.

The other approach employs the computer, and for that one must somehow specify 'natural products'. In a first approach to this the numbered answer set from the substructure search (containing the CAS Registry Numbers of all 391 compounds retrieved in that search) in the CA File was linked with '(L) (occur? or isolat? or isoln or extract? or identif? or formation? or formed or forming or natural)'. This gave 17 literature references. By entering the command 'SELECT HIT RN 1–17', the computer now extracts only those registry numbers from the 17 references that were among the total of 391 from the previous substructure search *and* that had been indexed with any of the keywords in the search profile. These 30 registry numbers can then be re-transferred ('crossover') to the Registry File and the corresponding compounds be displayed there. This 'advanced' example illustrates that CAS Registry Numbers are synonymous with compounds and form the common link of both the *CA* structure and literature files. It may happen, unfortunately, that natural product isolation is not indexed with any of the keywords used above, but rather as, e.g., 'from *Apium*

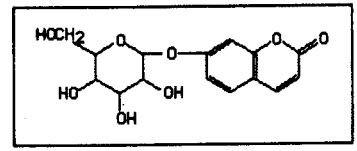
graveolens'. A check on the remaining compounds confirmed that this kind of indexing was indeed used; and at the same time that those relevant literature references were in the *CA* section 'Plant Biochemistry'. As a result of this finding and using the same techniques—with section title instead of keywords—a further 57 (!) naturally occurring coumarin glycosides were retrieved. I do not know of any other way this could have been done except by computer.

The same kind of search is simpler and more reliable in *Beilstein* online.[30] Because this database is also available on STN,[23] the input of the substructure is the same; you could draw the structure in either the *Beilstein* or Registry file and then use it for searching in both. In contrast to *CA* online (see above) *Beilstein* online contains structure, data and literature references in a single file, obviating transfers ('crossovers') like those described above. The substructure described above retrieved 403 coumarin glycosides in *Beilstein* for the period 1830–1979 (there is at present no way to limit the search to a certain time period as was shown above for *CA*). The natural products are conveniently selected by combining the answer set with 'AND INP/FA', meaning *I*solation from *N*atural *P*roduct/*F*ield *A*vailability. This retrieves only those 46 compounds that have a data field describing the isolation from natural sources in their record. Likewise, any collection of structures may be restricted to those having certain properties. Narrowing down further with 'ORP/FA' (*O*ptical *R*otatory *P*ower), only 31 compounds remain. One of them is shown in Fig. 4 with the relevant data. You may now display further data present for that compound, or alternatively look them up in the printed handbook using the reference shown in the *SO*urce data field (meaning supplement 5 (EV), Vol. 18 in Fig. 4). This search would not be possible in the printed *Beilstein*; it costs a total of DM105 ($60), including the substructure search fee of DM90 ($50) (academic institutions that subscribe to the *Beilstein Handbook* get a 50% reduction on the rates). With regard to the costs involved, you should continue searching the printed *Beilstein* for all questions that can be solved there, such as data on single fully defined compounds, provided your institution still


```
14 JUL 89 20:52:15                STN INTERNATIONAL                P002

L8  ANSWER 1 OF 31

BRN  1690562  Beilstein
MF   C15 H16 O8
SY   Umbelliferon-7.beta.-glucosid
FW   324.29
SO   5-18
LN   18941; 17647
```




```
Isolation from Natural Product:
INP  aus Trockenpraeparaten von Tee
     Reference(s):
     1. Mikaberidze et al., Chem.Nat.Compd. (Engl.Transl.), 8, (1972),
        234, CODEN: CHNCA8
        238
INP  aus Astragalus falcatus
     Reference(s):
     1. Alaniya et al., Chem.Nat.Compd. (Engl.Transl.), 8, (1972), 235,
        CODEN: CHNCA8
        239

Optical Rotatory Power:
ORP  -84.500 deg
     Type:   (alpha)
     Wavel:  589.00 nm
     Temp:   20.0 Cel
     Reference(s):
     1. Mikaberidze et al., Chem.Nat.Compd. (Engl.Transl.), 8, (1972),
        234, CODEN: CHNCA8
        238
```

Fig. 4. Coumarin glycoside retrieved from *Beilstein* online by a combination of substructure and data search. Reproduced by permission of Springer-Verlag.

subscribes to the handbook. For chemists who have problems in locating the volumes in which to find the desired compound, the program SANDRA[30a,35] obviates the need to know the *Beilstein* system.

SEARCHING FOR A REACTION, METHOD, CONCEPT, PROCESS

Example 3

Example 3, a method for effecting the *acetalisation of a hindered keto group in an α-keto ester*, poses a problem because

CA is compound, rather than reaction, oriented. A straightforward *keyword search*[36] gave 31 literature references in the STN *CA* File, which were reduced to zero when further specified with 'hindered or hindrance'. By checking indexing and titles all 31 were found to be irrelevant. A *substructure search* in the Registry File for all acyclic and cyclic ketals of α-keto arylacetic esters retrieved in April 1988 only 17 such compounds (out of 9 million!). Following this, 13 references were found concerning their preparation. Most were judged not relevant in this context (i.e. prepared by methods other than ketalisation) by checking title, indexing and abstract. Out of the few more promising ones looked up in the original publication one described the conversion of 4-acetylaminophenylglyoxylic acid to the dimethyl acetal with $MeOH/H^+$, and a 1983 publication gave a general method of ketalisation with $MeOH/Me_3SiCl$—here phenylglyoxylic acid reacted in 55% yield. The latter reference cites the 1980 Noyori paper found by a different approach in Chapter 1, Example 3. Fortunately many roads converge!

Since there are special printed sources for reaction information (see Chapter 1), there are databases devoted solely to reactions. The 'Chemical Reactions Documentation Service' (CRDS)[37] produced by Derwent and exclusively available via the host ORBIT Search Service[18] contains all information from Theilheimer's *Synthetic Methods of Organic Chemistry*[7a] (see Chapter 1) and the *Journal of Synthetic Methods*. The disadvantage of this online-searchable file is the lack of graphics.

In order to meet the growing need for more and better reaction information, CAS have been building a special reaction database, CASREACT, which was made available (exclusively on STN[23]) in spring 1988.[38] This has no printed equivalent and covers single- and multi-step reactions from ca 100 primary journals in the *CA* organic chemistry sections since 1985, constituting at present over 740 000 reactions steps from ca 58 000 references, with an expected addition of more than 170 000 reactions annually. In this database, every reagent and solvent is indexed and therefore searchable, whereas in *CA* they were only indexed if new or used in a novel way. Reactions in

CASREACT are searched via compounds (i.e. their CAS Registry Numbers) and their role (reactant, product, reagent, etc.) in the reaction; retrieved are literature references containing the reaction, not reactions themselves (see below); these can be displayed graphically from the references found. In this example, you therefore have to start with a substructure search for the product in the Registry File. The search described above was later (July 1989) repeated on a more general level, including α-keto acids as well as esters, to give an answer set L3 with 57 compounds. Only one of those was found to be present in CASREACT, and the search 'S L4/PRO' (compound in L4 as *PRO*duct) retrieved only one reaction which was displayed and found irrelevant: no ketalisation reaction (remember, we had not specified the starting material 'side' of the reaction).

We now come to the commercially available *in-house* reaction database systems REACCS, SYNLIB and ORAC[38,39]). These differ significantly from the hosts and databases discussed so far. With these you buy the system package (reaction databases and software for building and searching them) and run it on your own DEC VAX minicomputer. There are no usage-dependent costs as in 'classical' online searching; all you pay are the expenses incurred in running the computer and fixed annual licence and maintenance fees for databases and software. This is very attractive for large chemical companies who not only do a lot of searching, but want to build their own databases with confidential company information. Although 'academic programs' for all three systems are offered, not many universities have access so far to these excellent tools for training in both computerised retrieval and chemical reactivity studies. Owing to the special cost situation, access can be considerably more liberal than with online databases. All three systems have a graphic-oriented, menu-driven 'user interface', and are definitely more 'user friendly' than the other databases described here.[39] Our versions of REACCS and ORAC currently have stored about 130 000 and 40 000 reactions respectively, so it was not really surprising to find nothing useful concerning Example 3.

Example 4

In Example 4, where information on the *action of alkali metals in liquid ammonia on aryl sulphonamides* was required, a keyword search in the *CA* File again gave no relevant information, and a substructure search is not feasible for this kind of problem with a very general and common substructure. In contrast, REACCS and ORAC[39] both did provide potentially useful answers. In these systems the search for reactions proceeds basically by (sub)structures, plus their roles (as reactant, solvent, etc.) in the reaction. It is also possible to search for data such as yield and temperature, and with keywords. In REACCS, a sulphonamide group was drawn on the screen easily and speedily with a 'mouse' and the help of a menu and defined as reactant substructure. The result from a menu-activated search for all reactions with that reactant was combined with a second one for all those having ammonia as solvent. Because the reactions retrieved were specific enough, it was not even necessary to limit further to alkali metals as reagents. A more 'advanced' (and faster) query would have used keyboard commands instead of the menus: with the sulphonamide group on the screen, entering 'SSS (substructure) AS REACTANT AND FORMULA = H3N AS SOLVENT' does it all in one step. Either way, four reactions were found in the Theilheimer File (46 305 reactions from printed volumes 1–35; cf. Chapter 1), in all sodium was the reducing agent (see Fig. 5). A search with the same query in the Current Literature File with ca 25 000 reactions from the period 1983–88 gave another two reactions with lithium and potassium as reagents. A similar search in ORAC retrieved six reactions out of 40 000 in our present version of the database; one of these is reproduced from the terminal screen in Fig. 6. You will notice that this uncovered an unusual type of reaction—an example of how even the idiot computer can come up with serendipitous information in an online search, of the kind that in a manual search might easily have fallen by the wayside!

Example 4 was later also tried in CASREACT. As stated above, a substructure as common as the reactant 'aryl

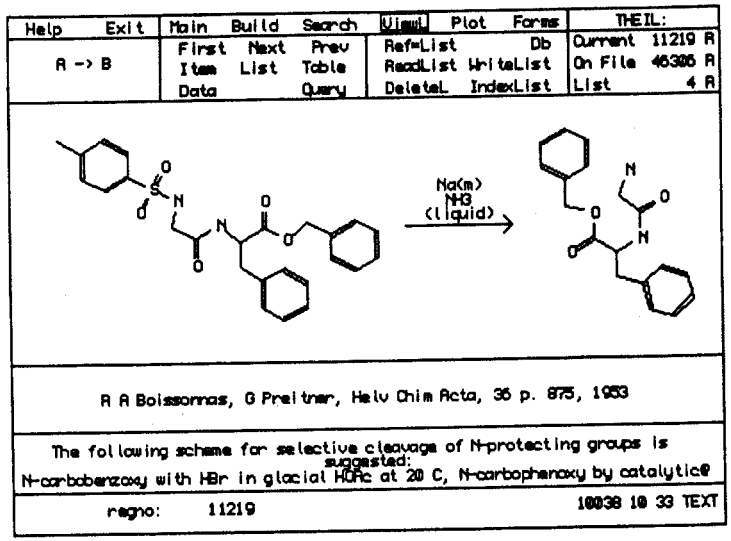


Fig. 5. Reaction display for action of alkali metals in liquid ammonia on aryl sulphonamides (Example 4) in the in-house reaction database system REACCS (Theilheimer File). Reproduced by permission of Molecular Design Ltd/S. Karger AG.

sulphonamide' cannot normally be run to completion within system limits. This is possible, however, when the structures are limited to those occurring in the CASREACT database while searching in the Registry File by adding a code ('screen') to the search profile with the substructure. The 3951(!) sulphonamides thus found in answer set L7 were then crossed over from the Registry File to CASREACT where 13 references (not reactions!) were retrieved with the profile 'S L7/RCT (L) 7664-41-7/SOL (L) (7439-93-2/RGT or 7440-23-5/RGT or 7440-09-7/RGT or 7440-17-7/RGT or 7440-46-2/RGT)'.

The registry numbers of the sulphonamides as *ReaCTants* are in set L7, the ones for the *SOL*vent ammonia and the possible *ReaGenTs* Li, Na, K, Rb and Cs are each specified with their role in the reaction; the (L) operator again ensures specificity by retrieving only those reactions that have all the given partners

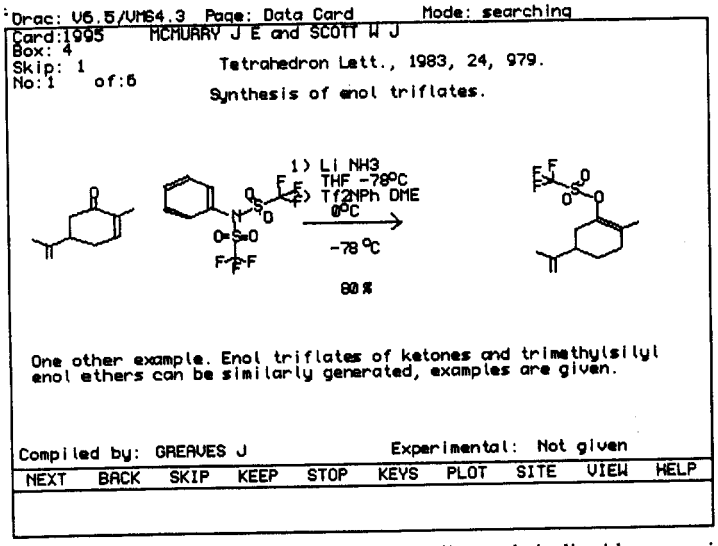


Fig. 6. Reaction display for action of alkali metals in liquid ammonia on aryl sulphonamides (Example 4) in the in-house reaction database system ORAC. Reproduced by permission of ORAC Ltd.

in the same step and not in different steps of a multi-step sequence. One of the reactions from ref. 10 is shown in Fig. 7. It is possible to display (or print offline, see above) all relevant reactions (there are 26 out of 33 found here!), but it is usually cheaper to print the references after checking just a few reactions for usefulness. The dependence on a previous Registry File substructure search (unless you look for reactions of single compounds only) is a weakness of CASREACT, because then you are often unable to answer general questions such as functional group transformations. This fault is aggravated by the fact that reacting bonds are marked in the display (see the asterisks on some bonds in Fig. 7), but cannot (yet) be searched for as in REACCS or ORAC;[39] this sometimes results in many irrelevant reactions. The total cost for Example 4 was DM370 ($205), including DM205 ($115) for the one substructure search (universities currently pay only 15% of the substructure search

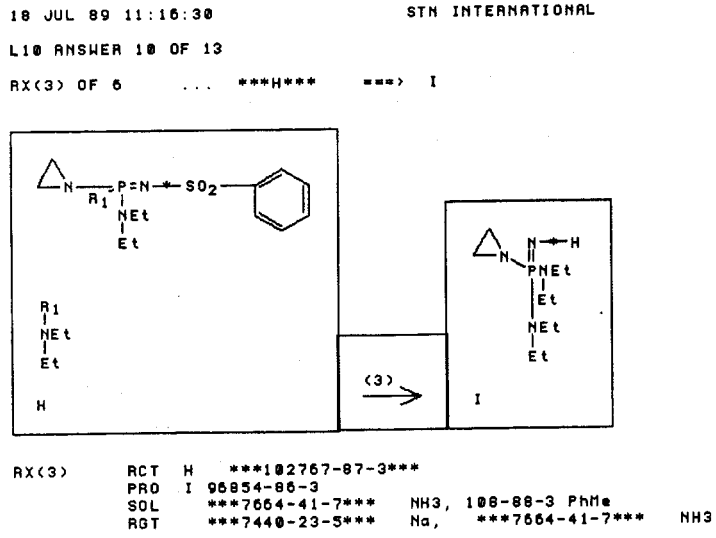


Fig. 7. Reaction display for action of alkali metals in liquid ammonia on arylsulphonamides (Example 4) in the reaction database CASREACT (STN; search terms framed by ***). Reproduced by permission of Chemical Abstracts Service, a division of the American Chemical Society.

fees, but they have to pay the full price for CASREACT itself). The strength of CASREACT is its thorough coverage of organic reactions (albeit only since 1985, see above); its annual increase is of the same magnitude as the accumulated total of reactions in all REACCS files! You should use it as a last resort if other printed sources and databases discussed here and in Chapter 1 fail to produce the desired results.

Concept searching via keywords[40] is problematic for two main reasons. First, when doing it online, as many spellings and variants as one can think of have to be included in the search profile, using search aids and print-out as described before. The other difficulty has already been discussed in Chapter 1 and is probably beyond solution. It is sometimes impossible to ascertain the exact terms in which the indexer had described the

concept you are looking for, even with the help of search aids. Worse still, he might not have indexed it at all, either because he did not think it important or the author of the primary publication did not. There is no point in discussing whether this was done on purpose (e.g. routine spectroscopic data) or erroneously.

In a search for the separation of enantiomers by capillary gas chromatography, three relevant references were provided by the chemist before the search, all of them dealing uniquely with that subject. None of them had 'capillary' in the title or in the *CA* indexing; using the term 'capillary' in the search profile gave highly relevant articles, but obviously missing some; leaving it out gave about ten times as many references but with most of them about conventional gas chromatography and thus not relevant. One of the characteristics of online searching is that it shows up deficiencies not only in the search process but also in the indexing. In a manual search in printed CA you would never have noticed this problem, because there you cannot check how a certain article was indexed by CAS.

A different *keyword-independent* approach to concept searching is provided by the *Science Citation Index* (cf. Chapter 1) and its online version SCISEARCH, available from DIALOG[17] and DATA-STAR.[24] This is based on later authors' citations of 'prior art' in the appropriate context, whether positively (i.e. he used it himself with success) or negatively (he found it did not work). Whether this is more reliable than indexing is a matter for judgement. More about the application of this method, as yet not utilised much by chemists, and the ideas behind it can be found in the documentation by the database producer, the Institute for Scientific Information,[41] or by its founder, Eugene Garfield.[42] Apart from using a completely different search principle, the *Science Citation Index* offers a more interdisciplinary coverage, albeit at the price of a less comprehensive coverage of chemistry than that provided by *CA*.

In a search for applications of the 'Baldwin rules' for the regioselectivity of ring closure reactions,[43] you will not get far when using *CA* online and even less when searching manually.

By looking for that author's special terminology 'exo' and 'endo' with 'trig' or 'trigonal', you will miss out even on key papers by Baldwin himself. On the other hand, on selecting the general heading 'Ring Closure and Formation' with the qualifications 'stereo' or 'regio' you will obtain a flood of references. A citation search based on the first five Baldwin papers[43] gave a large number of relevant references. To narrow this down, a 'co-citation' strategy was used, consisting of looking only for publications which cited *both* of the first two Baldwin papers.

TO SEARCH ONLINE OR NOT TO SEARCH ONLINE

Questions that can be well defined chemically, but are ill-defined with respect to the capability (access points) and coverage of information sources (see the *CA* search in Examples 3 and 4), cause problems with both the online and the manual approaches. Only experience and a certain amount of intuition as demonstrated for these examples in Chapter 1 can help you there. As a rule of thumb, the more general and/or less describable your question is, the more likely it will be that you will need several online 'sessions', with intermediate checking of the indexing, consulting search aids and thus iteratively optimising the search profile. Aiming at too much perfection can be dangerous too, and often you will have to make do with something less than perfect. Sometimes a look at a library catalogue for a good monograph is better than a lengthy and costly online search.[44] On the other hand, do not let the computer tempt you to do what is rightly called 'quick and dirty' searching.

Always be on your guard when you get *zero* answers. Often, chemists with preconceived ideas ('you know, I am first in this field, nobody has done anything like this before') run away happily from the terminal after such an 'affirmative' result and tell all their colleagues. It is convenient for them to forget that a misspelled keyword, a false logical combination, a missing space or one too many (very common, that!) might be responsible for hiding what really *is* there all the time. Do not put all

your trust either in the computer or in yourself. True, it is easier to find (or rather select) information by browsing through *explicit* information in a printed index than to predefine and first describe it in an abstract *implicit* way when preparing a search profile. In the end, the latter is much faster, however, and above all not subject to omissions caused by fatigue after hours of reading small print. We have recently seen significant improvements in search for data and reactions—*Beilstein* online and CASREACT—and there is more to come. But today's problems cannot wait for tomorrow's databases!

By way of a post mortem, let us return to Example 1. Most chemists with online search experience would have included all four ibuprofen Registry Numbers right from the beginning to get a result superior to that with the manual search. In Example 2, the online search was narrower and more precise in scope than the manual search described in Chapter 1. An online search for *all* publications on the (*E*)- and (*Z*)-isomers of the pentenoic acid, with print-out of bibliographic data and relevant index entries, would have given a more comprehensive result. Perhaps, though, one should not make these comparisons, because they take no account of time and effort. What is clear is that in substructure search online is far ahead, but one can make out a case like that in other respects too—most concept or compound class searches if there is no appropriate heading in *CA*, or else one with a surfeit of examples like 'ketones'. The search for enaminoketones mentioned above is a case in point; this and other examples have been described elsewhere.[22a,44a]

Another point in favour of online searching: it is hard to check on the thoroughness and validity of a manual search, particularly long after, because so many things are only implied, intuitive and not recorded. A print-out of an online search, on the other hand, is not only more presentable, but the entire process—choice of keywords, inclusion of different spellings, etc.—can be checked years after and if necessary repeated (I leave it to your imagination to detect certain disadvantages in this!).

Perhaps I have not convinced you entirely on the pros of online searching, but if you now have second thoughts about both pros and cons of either approach to searching the literature the main purpose of this chapter will have been achieved.

So, to get started with online searching, ask experienced colleagues (if there are any around), read the relevant literature,[19–22] solicit information from hosts and database producers (always with considerable scepticism toward their claims!), and try it out yourself.

3

Basic Safety Rules

1. The moment you enter a laboratory where any work is being done, whether by yourself or by others, **put on Safety Glasses**. This should become a conditioned reflex. Perhaps the best way to induce it is a system of on-the-spot fines which everyone is entitled to collect; the proceeds to go to some worthy cause like the coffee club.
2. At least once a day while in the laboratory stop and ask yourself what you would do should an accident or fire occur *at that moment*:

   Where are the nearest eye-flushing device and safety shower? Can you find your way there blind-folded? Do they work? Check them yourself!

   Where is the nearest fire-extinguisher? When was it last checked, and by whom? Is the checker still around, to accept responsibility, or has he 'checked out'?

   Where is the nearest sand bucket? Does it contain sand or cigarette butts? **Your laboratory should be decidedly out of bounds to smokers!**

   What emergency route is open to you from where you are working? You should refuse point-blank to work in any location from which there is only one way out.

   Where is the nearest protective mask? The location of these should be clearly marked—the most important one is a smoke mask.

   Are the gas cylinders secure? In an emergency it may be

necessary to move them away as quickly as possible, hence it is best to have them secured on movable carts rather than strapped or chained to the bench.

Where is the nearest gas main valve?

Which is the most direct route to a first-aid station?

What is the telephone number of the fire brigade?

3. *Medical treatment.* Few doctors have enough chemical or toxicological knowledge to be able to judge which is the best immediate treatment for poisoning, burns or injuries caused by a specific chemical. Many charts are available which suggest the best course of action in common cases, and these should be available at all times and shown to the doctor or nurse. In most large hospitals there is now a Poison Information Centre which can be reached at all hours, and its telephone number should be prominently displayed.
4. Do you always keep in mind that you can be held personally accountable for the consequences of allowing children and other unauthorised persons into the laboratory? That, incidentally, includes pets!
5. Avoid working alone, and never work in the absence of someone else in the vicinity who knows of your presence and is within shouting distance.
6. *Always tend to work in a hood.* In addition, work behind a safety screen if there is any element of risk. All organic compounds should be regarded as toxic on principle. Relative toxicity values should not be relied upon; you have no way of checking how much of each you inhale or handle during any specific period. *It is a part, and an essential part, of the good experimental technique which you want to acquire, not to handle or inhale any chemical you work with.* Also if you direct the work of anyone else, you are probably required by law to be fully aware *beforehand* of any risk involved!
7. *Overnight reactions* involving heating and/or reflux and/or stirring should be done in a Night Room. This should have a device cutting off electricity in case of interruption of the water supply. Plastic rather than rubber tubing should be used for water cooling. Wiring-on should be done with care. Leave a securely fastened note with your name, address and telephone number next to each experiment.
8. *Disposal.* It all depends on what is being disposed of, the state of the plumbing, the location of your place of work and the laws and regulations of your community and State. There are plenty of books on the subject. Just one basic point: whatever you want to throw away and whichever way you decide to do it can have far-reaching legal and other consequences for you personally, so be in the know! It is, however, the primary responsibility of your supervisor and of your administration to formulate clear and unambiguous disposal instructions and to assume full responsibility.
9. Every laboratory should have posted *on the outside* a list giving names, addresses and telephone numbers of people to contact in case of fire, floods and similar occurrences.
10. *Refrigerators and cold rooms.* These may malfunction and catch fire or explode at any time. It follows, by the laws of probability, that this is more likely to happen outside normal working hours which under normal circumstances make up no more than ca 25% of the total time (Yes—figure it out yourself! That should wake up those in charge who tend to economise by pensioning off the nightwatchman!). No open vessel should ever be placed inside. To make certain, light bulbs should be taken out and any other source of sparking should be eliminated.

With a few minor changes, these are the same ten commandments that appeared in the first edition of this book. Since then there has been a flood, if not an orgy, of exhortation on the subject, some of it ridiculous, some of it self-contradictory, and much of it exaggerated and thus counter-productive and in the nature of overkill. The book has been criticised for devoting 'only three pages' to the subject. The author believes that for the mature and reasonably experienced audience for which it is written, whose main shortcoming is more likely to be forgetfulness than ignorance or recklessness, three pages is enough, provided that they are fully taken to heart.

4

Running Small-scale Reactions in the Research Laboratory

GETTING YOUR WORKPLACE ORGANISED

Building a Framework

On starting work, most likely you will be convinced that you have far less space to work in than you had expected or hoped for. The way to cope with this is to think carefully about how to make the most of it. For example, from your undergraduate days you were probably conditioned to expanding your experimental set-up in a horizontal direction—now you should think about doing things as far as possible going either up or down. And even should you be so lucky as to have more space than you bargained for, it will not take you long to discover the advantage of compactness—or having as much as possible within reach of two hands without having to walk more than 3 ft in either direction.

Probably the best way to bring this about is to construct a framework system. This applies to the regular workbench, and even more to a hood ('fume cupboard' to the British), where you should do as much of your work as possible for basic safety reasons, and where inevitably proper space organisation is of utmost importance.

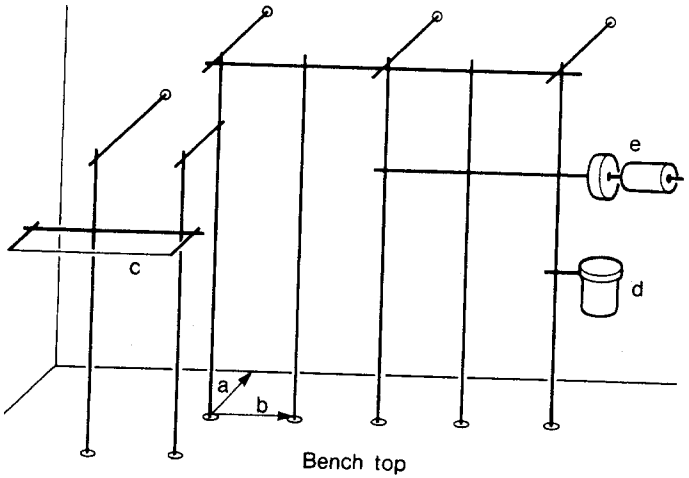


Fig. 1.

The arrangement shown schematically in Fig. 1 is based on the author's own experience and circumstances to be varied according to your own situation, preferences and vital statistics. Suggested dimensions are: $a = 20–25$ cm and $b = 15–25$ cm. Labelled components are (c) wire for holding flasks (e.g. chromatographic fractions), (d) beaker for holding pipettes, rods, spatulae, etc., and (e) suitable place for rolls of Parafilm, cleaning tissue or aluminium foil. One or two of the vertical rods should be higher (say 1.8 m) than the others, for holding fractionation set-ups or large chromatographic columns.

In a hood the main problem is corrosion. Even stainless-steel rods and fittings are affected in the course of time. The use of the glass-fibre composite rods now available should be considered.

A feature worth incorporating on one of the vertical rods, either on the extreme left or right, is shown enlarged for clarity in Fig. 2. This is for apparatus which is permanently assembled for frequent use, such as a rotary evaporator or a solvent distillation set-up, and where the only variable factor is its height. Very simply, the set-up is attached not to the vertical rod itself

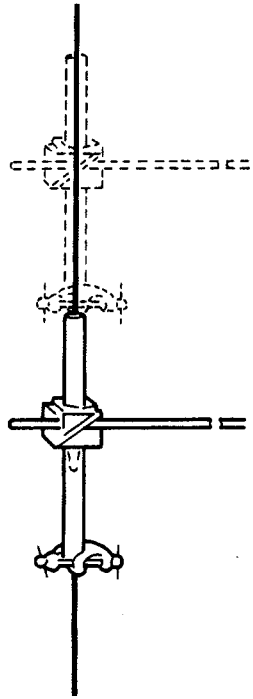


Fig. 2.

but to a metal tube which can slide up and down on the rod and is held at the desired height by resting on a clamp. The fact that the whole can be rotated sideways is usually an additional advantage.

The bottom feet attaching the vertical rods to the bench top should be as small as possible to minimise interference with apparatus. For this the usual support plates [Fig. 3(a)] should be sawn down [Fig. 3(b)]. One screw for attachment is sufficient. For side attachment to the wall, however, the full three-screw plates should be employed.

Cross-links between rods should not be lower than ca 40 cm up from the bench. Interconnectors should be as small and compact as possible [e.g. Fig. 4(a) and (b)]. Figure 4(a) shows

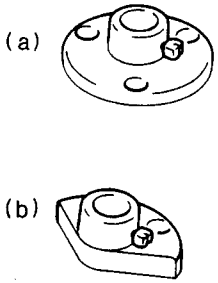


Fig. 3.

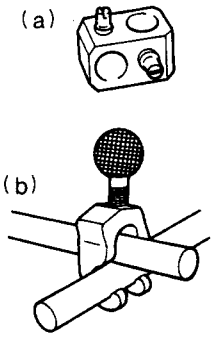


Fig. 4.

the type which if employed in a hood should be checked for corrosion as often as possible, because once the internal screws are stuck the connector as a whole cannot be removed.

Permanent or semi-permanent fixtures, such as safety flasks en route to water-pump vacuum, towers for drying or purifying gases or vacuum manifolds, should be attached as high on the framework as possible so as to minimise interference with work being done on the bench-top.

The standard framework systems which are available commercially are in most cases unsuitable for preparative organic chemistry. Their frame systems start some way up because in the main they are meant for use by physical chemists.

Making a Multiple Inert Gas Trap (MIGT)

It is difficult to think of any organic reaction that runs better when not conducted under an inert gas atmosphere. This usually means nitrogen, but argon is preferable in every way. In many laboratories one sees this problem 'solved' by an array of colourful and sometimes grotesquely (not to say Rabelaisian) shaped rubber balloons attached to apparatus (which is full of air to begin with, the hope being that somehow the air will leak out, but not the balloon's contents). This looks cheerful on colour slides and takes one back to one's childhood. However,

this will not do. It is a sobering experience to consult a suitable source of reference and find out just how permeable rubber is to oxygen and in particular water vapour, especially the thin variety used for toy balloons.

Figure 5 shows an apparatus that can be made by most glass-blowers. Based on a simpler trap originally described by

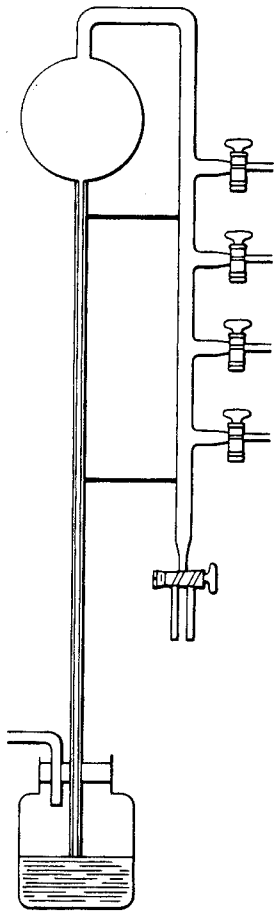


Fig. 5.

Johnson and Schneider,[45] the version shown will allow you to run several reactions under inert gas at the same time, or alternatively to store one or more reaction systems or containers with exclusion of oxygen and moisture, until used at a later stage. The thick-walled capillary tube (2 mm i.d.) on the left dips into a mercury reservoir (ca 10 mm head of mercury), and has to be 85–95 cm high. This leads via a safety bulb to a vertical manifold with three to five outlets, ending in a three-way stopcock which will allow for either evacuation or admission of inert gas. The mercury reservoir must have an outlet leading to a hood. When evacuating, care must be taken to have open only the outlet concerned, with the others closed. Since the apparatus as a whole is rather fragile, the two vertical tubes are best connected by one or two fused-on bridges and mounted (not too tightly) on a wooden board.

The tubing connecting the outlets to reaction systems has to be of the right sort. Unfortunately, what are called high-barrier elastomers [poly(vinylidene chloride) or polyacrylonitrile copolymers] do not seem to be available in the form of flexible tubing, and thickness may have to make up for inferior properties in other materials. Hence one has to compromise between thick-walled polyethylene or natural rubber pressure tubing (rather heavy) and rubber latex pressure tubing (much lighter but expensive and deteriorates more rapidly).

There are four great advantages in using this apparatus as a matter of routine: (a) the way it allows alternative evacuation and filling with inert gas makes the absence of oxygen and moisture almost certain and complete, (b) it allows the addition of reactants and reagents against inert gas pressure, thus preventing simultaneous entry of oxygen and moisture, (c) it saves on inert gas because once the system is filled no more need be passed in except when the internal pressure drops (as indicated by a rise of the mercury column) and (d) with proper attention (opening and closing the right stopcocks!) several reactions can be run on this apparatus at the same time.

The whole set-up can form an integral part of the framework system (Fig. 1) and if so it should be on either the extreme right or left.

CONDUCTING A SMALL-SCALE REACTION UNDER INERT-GAS CONDITIONS

The Basic Set-up

To a solution of M (516 mg, 1.1 mmol) in T (anhydrous, 6 ml) was added under nitrogen a solution of N (115 mg, 1.25 mmol) in T (anhydrous, 7 ml) dropwise and with rapid stirring during 0.5 h, keeping the temperature between x and y °C, after which the whole was allowed to reach room temperature during 1 h. It was then heated under reflux for 1 h, after which it was cooled and ice was added.

This is the kind of experimental procedure that you will see routinely in almost every issue of any journal in organic chemistry. Not many beginning researchers, not all advanced ones, and probably not many of those who actually write up these procedures know exactly how best this is done. In most cases it is not they who are entirely at fault, but it is because of the absence of the right sort of equipment. For that one should blame the manufacturers of scientific glassware.

In other words, your glassblower is someone whose friendship you will do well to cultivate in the future.

The general set-up to use is shown in Fig. 6. Flask A is the kind that will enable you to carry out small-scale reactions volume-wise, and still be able to measure the temperature *inside* the reaction mixture. The most useful sizes are of 50 and 100 ml total volume. The former can be used down to 5 ml actual volume, the latter up to 65 ml. These were formerly known as sulphonation flasks and then available in much larger sizes. Since the appearance of the first edition of this book they have reappeared on the market, this time quaintly under the name 'European style'. The best joint sizes are B19 or B24 in the centre and B14 at the sides. B is an equilibrated addition funnel, and such are available commercially in small sizes. The condenser (C) should be as short as possible—on this kind of scale the amount of cooling surface needed is very small. D is a drying tube connected to an outlet of the MIGT. G is the magnetic stirring motor (of the non-heating variety). H is not part

of the stirrer but in fact is a pile of thin plywood plates whose removal or addition will cause the heating or cooling bath to be raised or lowered. If there is a simpler way of 'keeping the temperature between x and y °C' without interrupting the magnetic

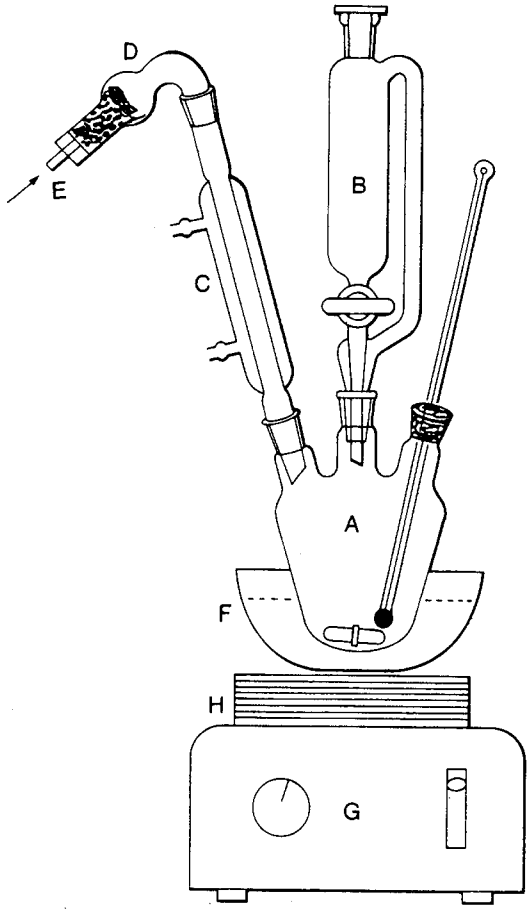


Fig. 6.

Note: The arrow in this and subsequent illustrations indicates points of attachment to the multiple inert gas trap (MIGT)

stirring, I should like to know about it. Naturally this means that there will be some distance between the motor and the bar inside the flask, but the effective range is usually 5 cm and magnetic stirring is generally more steady at some distance than close by.

With this set-up, and always when using an addition funnel, one basic warning is needed: the stopcock should be well-greased *and* it must not be clogged by grease. This is best ensured by connecting the stopcock outlet briefly to vacuum. There are few greater disasters than being all set to start, with reagent, solvent and reactant in place, and then discovering the blockage!

What Size Flask to Use

As a general rule, the total contents (i.e. after everything has been added) should never exceed 40% of the flask's volume. There are two good main reasons:

1. forestalling eventualities, such as foam, the ever-lurking enemy, and sudden exothermic events which can more easily be brought under control when the flask is less full,
2. making it possible to do the working-up (Chapter 5) in the reaction flask itself; for that you need additional volume.

When in doubt, and when you simply do not have the size to fit the above, your golden rule should be that it is better to have the flask too big than too small.

The Basic Procedure

Flaming-out

The apparatus is connected to the MIGT as shown, with A and B stoppered. If the thermometer is of the low-temperature type it is best inserted later. The substrate may already be placed in A and the reactant in B if they are not too volatile. Water-pump

vacuum is then applied via the MIGT; and using a Bunsen burner or heat gun (also known as a hair dryer and much cheaper under that name!) the apparatus is heated gently, starting at the extreme ends including the addition funnel and working towards the exit E. The desiccant in D should be heated more strongly. The system is then allowed to cool and inert gas is admitted.

Working at or Below Room Temperature Only

In such a case there is naturally no need for a condenser, and a flask and adapter as shown in Fig. 7 greatly simplify matters. The thermometer-cum-drying tube adapter offers the advantage of an unobstructed view of the entire temperature scale. For that reason it is particularly suitable for small-scale low-temperature work, and a two-necked flask can be used.

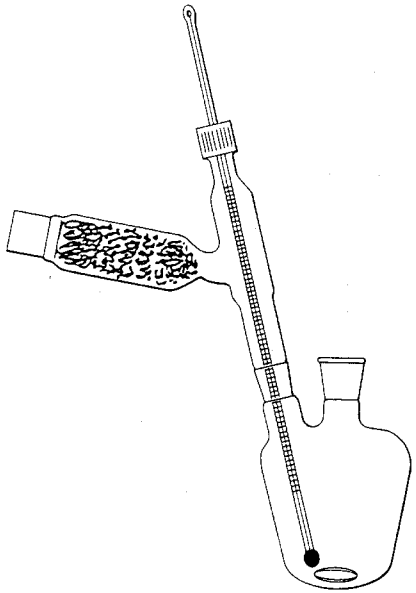


Fig. 7.

Introducing Anhydrous Solvent (Tetrahydrofuran, Diethyl Ether, Dioxane, Dichloromethane, etc.)

On a small scale these are best introduced directly into the reaction flask against inert gas pressure via a small cylindrical addition funnel (previously flamed out) containing active alumina. The latter is the usual grade I material which has been further activated by heating in a high vacuum at 300 °C (metal bath) and thereafter stored in small bottles with a rubber-stoppered narrow neck. The arrangement as a whole is illustrated in Fig. 8. The funnel outlet should be drawn to a fine point so that no water vapour can get in between additions. Naturally it will also serve to introduce solvent into the addition funnel (B) (Fig. 6) to dissolve the reactant.

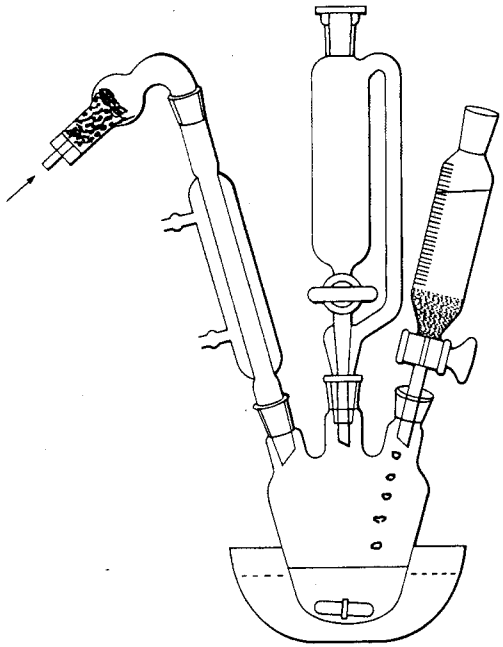


Fig. 8.

The amount of alumina should be of the order of 0.4–1 g per 10 ml of solvent in the case of tetrahydrofuran, acetonitrile, 1,2-dimethoxyethane or dioxane, and less than half that with diethyl ether or dichloromethane. The alumina will of course retain any stabiliser (such as butylated hydroxytoluene) which is usually added to ethereal solvents.

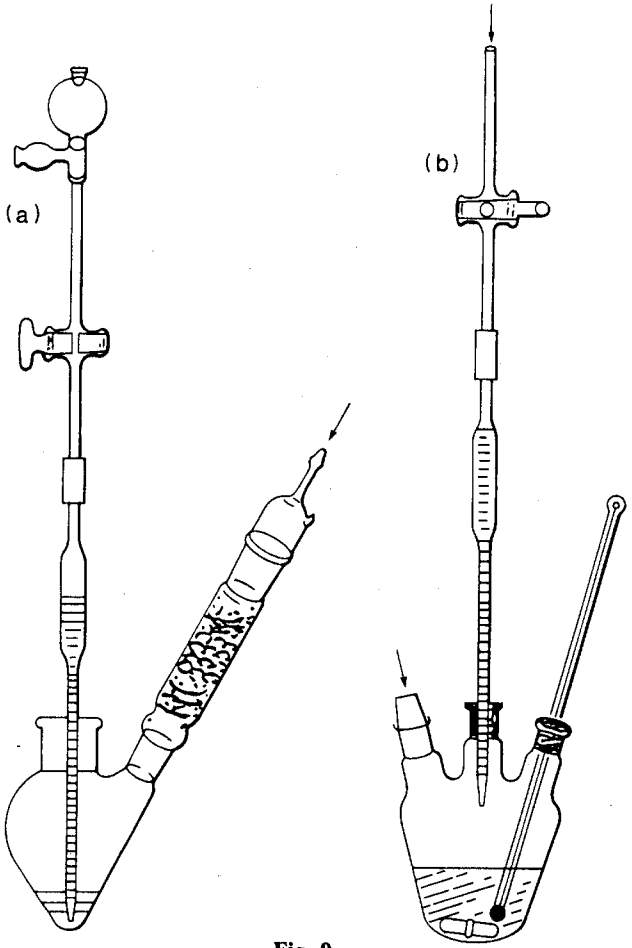


Fig. 9.

On a really small scale, and when a small enough equilibrated addition funnel is not available, the procedure shown in Fig. 9 is a useful variant. The addend is first dissolved in a small pear-shaped two-necked flask, and then drawn up into a delivery pipette connected to the pipette filler via a capillary stopcock [Fig. 9(a)]. The filled pipette plus stopcock (now closed) is then inserted into the reaction flask, the stopcock is attached to the MIGT and the contents are added dropwise to the reaction mixture by cautious opening of the stopcock [Fig. 9(b)].

Heating and Cooling

With a bath like F in Fig. 6, the handiest way of heating is by means of a small single-coil immersion heater connected to a variable resistance [Fig. 10(a)] which may incorporate a thermostat device. These may have to be home-made; the commercially available ones [Fig. 10(b)] are suitable only on a larger scale.

As for cooling media, there are many possibilities, ranging from ice–water to various solvents cooled by dry-ice or liquid nitrogen (liquid air should not be used for safety reasons). A large list of suitable combinations is given in *The Chemist's Companion*,[46] all involving solid CO_2 or liquid nitrogen and a slush of the liquid in equilibrium with the frozen material. Some cautionary remarks are appropriate here. The temperature quoted is always the very minimum attainable, and inside the

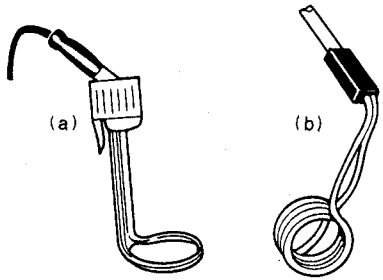


Fig. 10.

flask it will always be 5–10 °C above that, even when disregarding any possible reaction isotherm. Thus the effective temperature for $CO_2 + CCl_4$ is -15 °C and not -24 °C, that for chloroform and liquid N_2 is -50 °C and not -64 °C (just fine for reactions in dimethylformamide which would always be frozen if what the tables say were true). And as for that ubiquitous piece of fiction, '-78 °C', the lowest effective temperature attainable with solid CO_2 and any solvent liquid above -90 °C and remaining reasonably fluid (methanol, isopropanol, acetone, ethyl acetate, etc.) is ca -70 °C. If a lower temperature is really required with such solvents, or where a reaction isotherm has to be kept in check, this is best achieved by judicious addition of liquid N_2 to the solvent–CO_2 combination. Incidentally, another excellent solvent to add to that list is *tert*-butyl methyl ether (TBME), discussed elsewhere in this book; it does not become viscous above the freezing point, is not hygroscopic, is easily dryable for re-use and is stable (no peroxides!); all this in addition to the fact that it is now among the cheapest of all organic solvents.

When a low temperature has to be sustained for any length of time it is necessary to use an insulated bath. The shallow Dewar flasks now on the market are expensive and easily prone to breakage. Also, their height and the metal enclosure used for protection will make it difficult to use magnetic stirring. A simple and most inexpensive alternative is illustrated in Fig. 11. The two nestling dishes are of glass, or better still of polypropylene or polycarbonate, the type you can usually find in various sizes in kitchenware stores or even supermarkets. The space between them is best filled with polyurethane foam using the

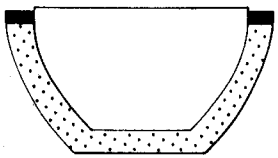


Fig. 11.

two-liquid combination or spray now commercially available (when doing this the dishes have to be separated by some spacer, with a weight on the upper one otherwise it will float up while the foam is forming). After hardening, the excess foam is cut off and the exposed rim protected by epoxy adhesive.

Other Means of Adding Reactant or Reagent

When a sensitive reagent solution, such as an alkyl lithium or Grignard reagent, has to be added in small amounts, there is no point in first transferring it to an addition funnel. Instead (and this really applies to all dropwise additions of liquids in small-scale work), it is worth constructing an addition burette as shown in Fig. 12. The capillary outlet of this (i.d. 1 mm) has a length of ca 10 cm, which allows for filling as shown in Fig. 13 from a storage bottle, keeping the latter under a gentle stream of inert gas. Here the advantages of the MIGT come to the fore: the various outlets serve at the same time for this and for connection to the reaction system, and also to the top of the addition burette while the reagent is being added so as to equalise pressure. Such addition burettes can be of 5, 10 or 25 ml total capacity.

When a Reagent is Best Added as a Solid

When the addend is a non-hygroscopic solid and is reasonably stable, it may be of advantage to add it in small portions rather than in solution. This will keep the total volume to a minimum (desirable in all but unimolecular reactions) and will prevent complications with a hygroscopic solvent such as tetrahydrofuran (THF).

This is also advisable where prior preparation of a solution involves some risk, such as with lithium aluminium hydride (inverse addition) or aluminium chloride. Here the reagent is quickly weighed out in a stoppered vial and kept there between additions. The rate of addition should be monitored by following the temperature of the reaction mixture—if there is no

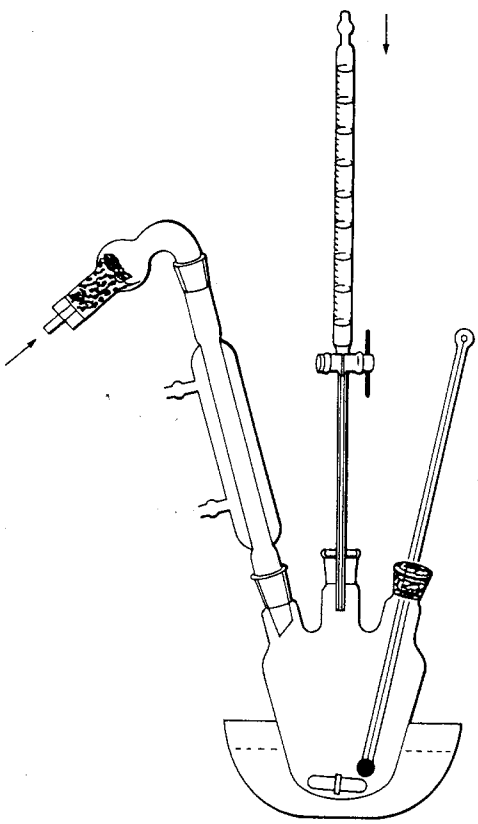


Fig. 12.

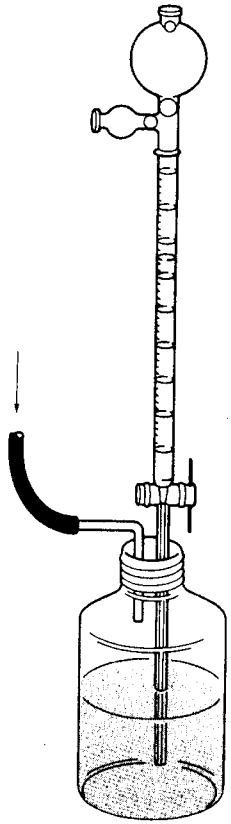


Fig. 13.

change it usually means that the temperature is too low (and reagent concentration may build up towards an uncontrollably exothermic reaction), and it should be raised before further additions are made.

When a Reagent is Best Added in Solution

Many sensitive reagents can be bought in solid form, particularly bases such as sodium methoxide, potassium *tert*-butoxide and lithium isopropylamide. However, these are usually prepared in solution to begin with and then the solvent is removed under circumstances over which you have no control. If you prepare such solutions yourself you know what you have, and can in most cases standardise them and dispense them by volume which is faster and surer than weighing out. A typical example is sodium methoxide in methanol (up to 4 M concentration). If the reagent will be needed in solid form after all, it will be possible to remove the solvent, either *in vacuo* or as an azeotrope.

In other cases the reagent, although available in its original state, is so reactive that it is more practical and safer to have and add it in solution. Examples are all alkylaluminium reagents and diethylzinc (best kept in toluene or heptane or, even better, cyclohexane), titanium tetrachloride, tin(IV) chloride, the boron halides and bromine (best in dichloromethane or carbon tetrachloride). Such solutions are best made by rapidly adding a roughly known volume to a weighed volumetric flask, weighing again and then diluting to the mark with the dry solvent. The same procedure should be used when having to add a catalytic amount of a sensitive reagent (transition metal complexes, crown ethers, BF_3–etherate, zinc chloride); dosage by volume is more reliable.

Frequently such solutions can be bought but you should do so only if the contents are known in terms of molarity. All too often suppliers still give content on a percentage basis without even giving the specific gravity (and then add insult to injury by warning you not to expose the contents!).

When there is just no alternative but to weigh out accurately the reactant which is the sensitive one (typical example: sublimed potassium *tert*-butoxide), the course to follow is roughly and quickly to weigh out in a tared container first on, e.g. a digital balance, then to weigh accurately with the container closed, and then adjust the quantities of all other reactants accordingly.

Concerning Magnetic Stirring

The choice of the right kind of stirring bar can be crucial. Problems usually arise when the medium is viscous and/or inhomogeneous. Then, and always when you are not sure what is going to happen to the consistency of the reaction mixture in the course of a reaction, it is advisable to use a bar which is short and compact and thus has maximum torque. Two such versions are shown in Fig. 14(a) and (b). Both have what is important, namely a pivoting point, although that shown in Fig. 14(a) has one which is usually removable, which can cause trouble when it happens in the middle of a reaction. The second type ('American football') is now obtainable in small sizes (length down to 10 mm), the 16 mm size is perfectly suitable for volumes up to 100 ml. The one shown in Fig. 14(c) should be avoided; it is good only for beakers.

Above all, one should aim for steady rather than rapid stirring. This will avoid losses due to splashing, and can usually be ensured by finding the right position and height above the stirring motor.

Frequently it is advantageous to stir a heating bath, both to prevent local overheating and to help along the bar in the flask. For this you need something that will take up as little space as possible. The best solution is the common paper-clip, the inside of which is slightly bent upward [Fig. 14(d)].

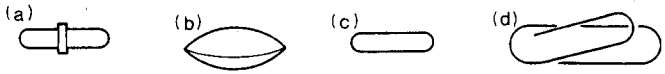


Fig. 14.

On the Importance of Being Temperature-Wise

The paucity of the right kind of small-scale glassware leads to a situation where, let us face it, most researchers do not actually measure temperatures inside a reaction, at any rate low temperatures. That is the real origin of '-78 °C'. That situation is most undesirable and leads to virtual irreproducibility of

experimental results in many cases. Moreover, there is the basic fact that the most significant indicator of whether a reaction occurs on adding A to B is a change in temperature.

The problem is not just that of suitable glassware. There is a well known extension of 'Murphy's law' which states that the part of the scale of the thermometer which is crucial to the experiment is the one hidden behind the stopper. If only more thermometers were made (and used) with scales that begin well above the bulb and which are corrected for a reasonable (say 1 cm) immersion instead of the usual 7–10 cm! From all the information available to this author, such desirable changes would make little difference to the price. Other aggravations: scales which become invisible owing to leaching out of the pigment, and bulbs of ridiculous sizes and shapes. One way to solve most of these problems is to use the dial-type stainless-steel thermometers now available for the laboratory (and not just for the roast in the oven!), for use up to 250 °C or even higher, and even more conveniently down to -100 °C. Their accuracy may not be that high (usually ± 2 °C), but in most instances that is enough for synthetic work. That, and their relatively high price, are more than compensated for by their specific advantages: resistance to breakage, the very small space occupied by their business end and their readability.

As for thermometers of the regular kind and in particular the alcohol-filled type, do remember to store them upright at all times. Whatever the manufacturers may tell you, a broken thread cannot be reconnected in most cases.

Concerning Drying Tubes

You can definitely do without the sort shown in Fig. 15(a) unless you are the sloppy type who forgets to turn on the cooling water in the condenser. This kind breaks easily and is awkward to connect to the MIGT. The straight [Fig. 15(b)] or sturdy curved [Fig. 15(c)] types are the ones to use. The best desiccant is silica gel of the self-indicating type, and a supply of this and the drying tubes themselves should be kept in an oven about

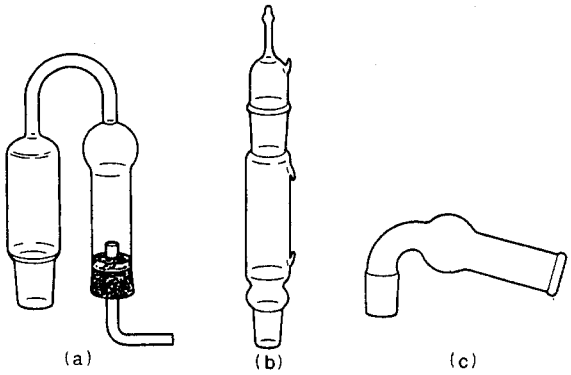


Fig. 15.

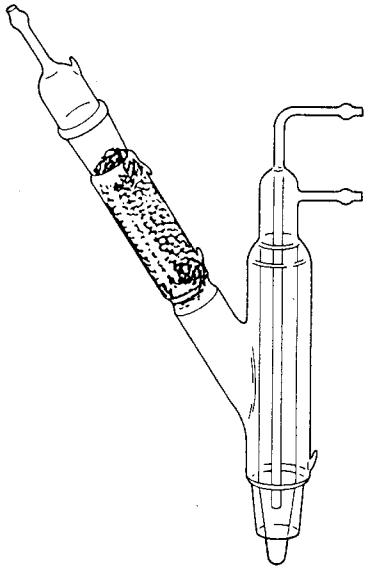


Fig. 16.

100 °C. The condenser-cum-drying tube shown in Fig. 16 is a useful piece of glassware so long as you remember that the cooling surface is limited.

Concerning Connection Adapters

More often than not you have no choice but to use bits of apparatus with different joint sizes, so that connection adapters have to be employed. That means elongating your set-up and increasing the internal surface and total weight, all of which are undesirable. A simple way to avoid this or at least cut it down to a minimum is to substitute the Teflon rings shown in Fig. 17, machined inside and outside on a lathe to the requisite dimensions. If this is done well they can even hold a moderate vacuum. The only snag is sometimes taking them out again, but this problem can be surmounted by using the contraption shown in Fig. 18, which is known as a 'reverse hammer' by dentists,

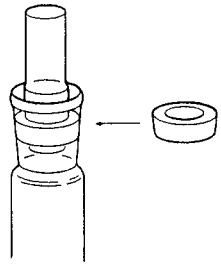


Fig. 17.

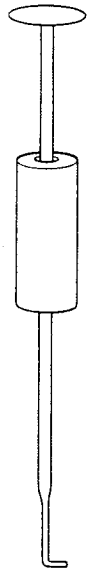


Fig. 18.

who use it to remove old crowns. The way to use it in this instance is to hold the stem (below the 'hammer') in one hand, place the bottom hook below the Teflon ring, and sharply push the 'hammer' up to the top plate with the other hand. These rings, of course, only solve the problem of reducing, and not of enlarging, adapters.

Coping with Other Experimental Procedures

The viscous reaction mixture was stirred at 80 °C for 1 h, after which it was cooled in an ice-bath and decomposed with ice.

Here one cannot avoid the use of an overhead mechanical stirrer as shown in Fig. 19. A Lubriseal joint in the centre neck is highly recommended; it should be lubricated by applying to the top a drop of silicone oil (not grease). Here you can see again the advantage of the special type reaction flask, in the way it allows a thermometer to reach far down even in such a case.

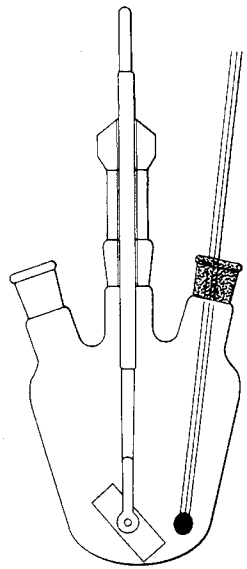


Fig. 19.

When the above procedure is followed to the point of ice cooling, then the reaction mixture will become much too viscous for stirring. One should raise the stirrer above the reaction mixture before cooling, and then stir the ice above so that decomposition can proceed downward. This applies, for example, to a polyphosphoric acid acylation or to a Friedel–Crafts reaction.

The clear solution thus obtained was then transferred under inert gas pressure to an addition funnel (or three-necked flask, or storage bottle, or onto dry-ice).

This is where a twice-bent tube of the kind illustrated in Fig. 20 should be used. The lower end is wider and filled with glass-wool in case filtration is necessary. The rubber stopper has two holes, closing one of which with one's finger creates the internal pressure needed for transfer. Before doing this the tube

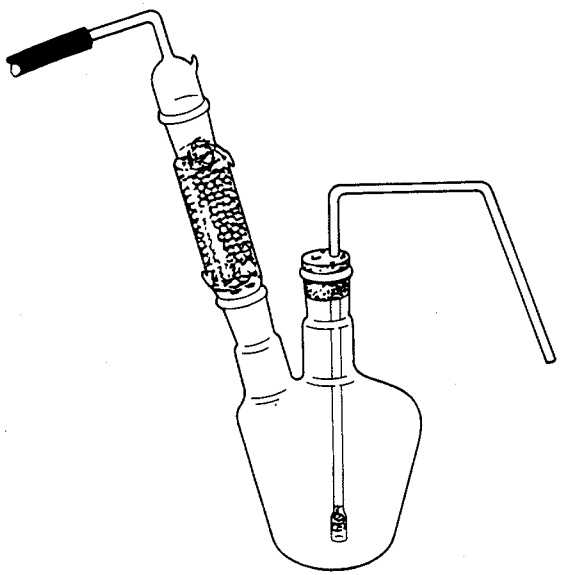


Fig. 20.

should be raised to allow flushing with inert gas beforehand, and for this the tube should be lubricated slightly with silicone grease. Also, it is usually necessary to push the magnetic stirring bar aside to allow the tube to pass right to the bottom.

There is little advantage to using a double-ended needle or cannula. In the device shown here you can at least see what is happening, especially if there is a blockage.

The solution was heated under reflux for 2 h, after which it was concentrated by distillation to one third its volume.

Earlier, the desirability of going up instead of sideways was mentioned. The adapter shown (Fig. 21) is fitted between the reaction flask and condenser. The small joint is for a thermometer if needed. The bore of the stopcock has to be wide enough to allow exit of air (or rather inert gas) and thus entry of distillate.

Naturally, this adapter is useful in any situation where solvent is first heated under reflux (e.g. over calcium hydride for drying), and then distilled.

To a suspension of sodium hydride (from 0.62 g of oil suspension, 12.9 mmol) in anhydrous THF (6 ml) there was added ....

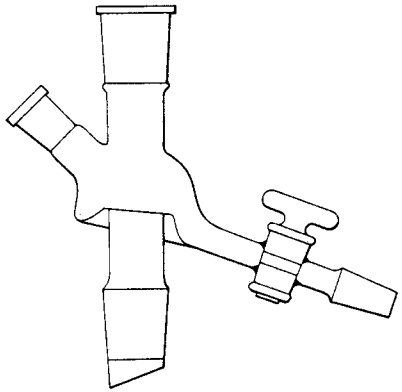


Fig. 21.

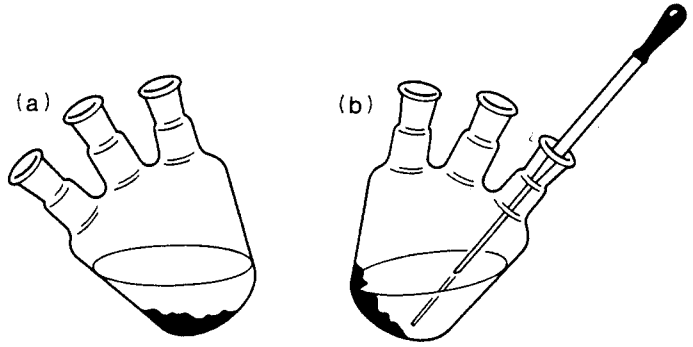


Fig. 22.

Proceed as follows:

1. Flame-out and cool as described before.
2. Introduce the weighed amount of sodium hydride and enough pentane to cover it.
3. Stir for 1–2 min and then allow to settle with the flask tilted to one side [Fig. 22(a)].
4. Carefully tilt the flask to the other side and withdraw the pentane by pipette (against inert gas pressure) [Fig. 22(b)].
5. Repeat this washing twice more, and then add dry THF as previously.

The same procedure should be used with potassium hydride. There in particular the washings must be carefully neutralised by adding isopropanol, otherwise a fire will inevitably occur later. Incidentally, as will be pointed out in another context, complete removal of the protecting oil can be checked for by allowing a drop of the washings to evaporate on the ground glass of the flask joint—if anything is left, it will show up immediately.

The solution was then heated under reflux under a Dean–Stark trap ....

The object is to remove water in the course of the reaction, and in small-scale work (10 mmol water = 0.18 ml) the commer-

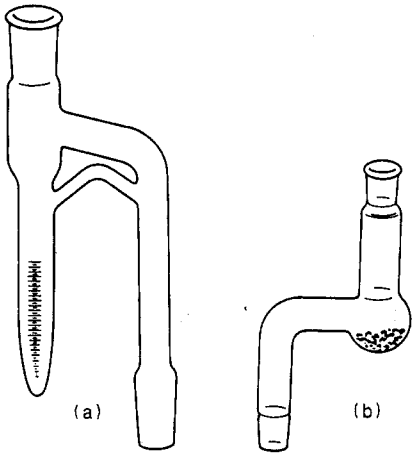


Fig. 23.

cially available Dean–Stark traps [Fig. 23(a)] are ridiculous. The adapter shown in Fig. 23(b), placed between the reaction flask and the condenser, is not only more appropriately sized but really does its job of removing water completely by the bed of molecular sieves. These can be activated *in situ* during the flaming-out process, and for this that part of the apparatus has to be heated more strongly.

The crystalline solid which was formed was filtered off under nitrogen, dried in a high vacuum and stored under nitrogen below 0 °C.

This is where our standard set-up will allow you to simplify matters. Against inert gas pressure the supernatant liquid is withdrawn by capillary pipette, after which more of the same anhydrous solvent is added by the standard procedure. After stirring, the solvent is again withdrawn. This is, of course, on the assumption that the product is indeed insoluble in that solvent, otherwise another one has to be chosen, or the entire operation performed in a cooling bath. When the washing process is complete (little or no residue on evaporation on the joint), the flask is stoppered and, with *gentle* stirring, vacuum (water

pump) is carefully applied. Inert gas is then re-admitted and as rapidly as possible the condenser is replaced by a stopcock [Fig. 24(a)], through which high vacuum is applied through the MIGT. After the material is judged to be dry, inert gas pressure is again applied, the flask is tilted and opened, and through the centre neck with the aid of a bent spatula the solid is broken up [Fig. 24(b)] and scraped into a bottle or vial. The latter is best closed with a rubber stopper, or a screw cap additionally closed with Parafilm.

X gas is passed into the stirred solution below 0 °C until precipitation of the product appears to be complete.

The most frequent problem here is clogging of the gas inlet tube, and some way has to be found to clear passage through it at frequent intervals. In Fig. 25 this function is performed by the thermometer, which is supposed to be there anyway. This is held inside the T-type inlet tube by a slightly lubricated sleeve of latex pressure tubing; a similar sleeve holds the inlet tube in the flask neck. The keyword here is flexibility—of course you can buy an inlet tube with a standard joint, but what are the chances that it will always immerse to the right depth in every experiment?

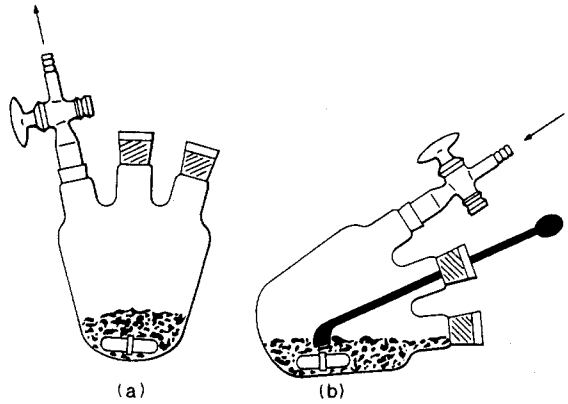


Fig. 24.

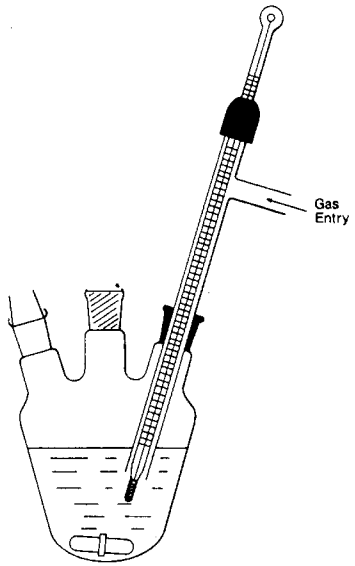


Fig. 25.

ON HOW NOT TO CONDUCT A REACTION UNDER INERT-GAS CONDITIONS

And now a few words on that ever-green topic. Figures 26(a) and (b) show arrangements that have been suggested recently for conducting a reaction under an inert atmosphere. In Fig. 26(a) inert gas is passed in at the top of the condenser, to bubble out again a short distance above through a gas bubbler. It seems that whoever thought this up lives in hope that in the course of time the inert gas will somehow find its way by diffusion into the reaction mixture below. Or perhaps he had resigned himself to the fact that part of his reagent, that which will be decomposed by the oxygen originally present, is expendable? In the second arrangement, that shown in Fig. 26(b), inert gas is passed into an inlet in the stirrer joint just above the reaction mixture, and exits, once again, through the top bubbler. Here the question is

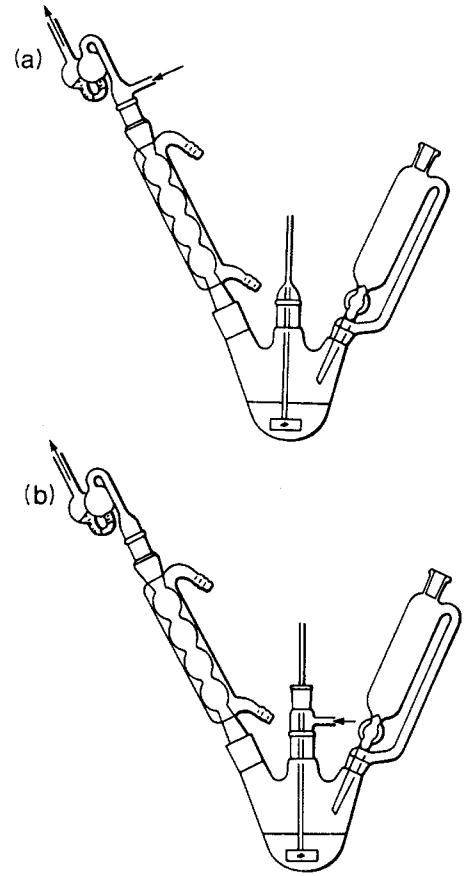


Fig. 26.

merely just how much time will pass until all the solvent has disappeared.

Both of these versions are, of course, also wasteful on inert gas. Another question to be asked is, 'where does the thermometer go?' With that kind of flask, with its time-hallowed shape, even if one neck were free, the thermometer would either be broken by the stirrer or else would measure the temperature

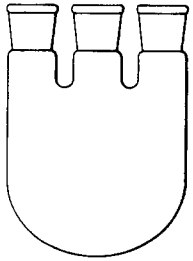


Fig. 27.

in the empty vortex caused by the stirring action. Flasks of the type shown in Fig. 27, which are commercially available, do in principle solve that problem, but only down to a 500 ml size. For anything smaller there would be no room for the clamp holding the centre neck. Hence there is really no alternative to the type of flask shown in Fig. 6 when working on a small scale.

CONDUCTING METAL–AMMONIA REDUCTIONS

The apparatus routinely used for this purpose is as suggested in Fig. 28. The special solid carbon dioxide condenser should be of a size which is commensurate with the flask used and may have to be made specially. The drying tube for such reactions should contain sodium or potassium hydroxide pellets, and never silica or calcium chloride. Connection to the MIGT and the flaming-out procedure, with the substrate in the flask, and also introduction of anhydrous solvent (usually THF or diethyl ether) is as previously described. Cooling medium (methanol or acetone) is then placed both in the bath and in the condenser and, after adding solid carbon dioxide and/or liquid nitrogen to both, ammonia is passed in until condensed to the desired volume (mark on the flask before the whole is assembled!). For drying the ammonia it has always been found sufficient to pass it through two towers in series, the first containing sodium hydroxide pellets and the second calcium oxide lumps and finally a

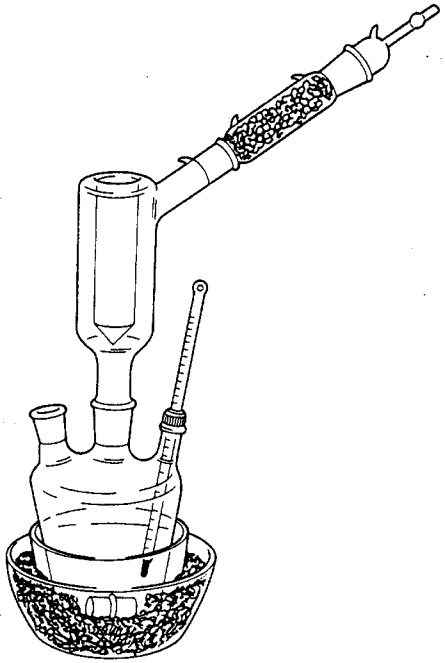


Fig. 28.

layer of granular calcium hydride. The emerging ammonia is at least as dry as that distilled from sodium in another flask. Direct pouring in from a cylinder is decidedly not advisable, as one might be tempted to do when working with larger quantities, the condensation of which may admittedly take some time. The moment the ammonia cylinder is closed inert gas pressure must be applied, and maintained throughout if and when a protic solvent and of course the metal used for reduction are added.

At the end of the reaction the flask may be opened to the atmosphere and the ammonia allowed to evaporate overnight—in a hood, of course. It is preferable, however, to remove both the ammonia and the solvent (usually THF, water-miscible and hence lowering the yield on isolation unless

removed anyway) *in vacuo*, naturally using a water pump. At the beginning of this care must be taken to avoid 'boiling over'. The completion of this process is best indicated by the fact that the inside temperature has reached ambient; cautious warming with luke-warm water is permissible but has to be monitored, as the bulb of the low-temperature thermometer may burst.

Teflon magnetic stirring bars used in such reactions inevitably turn black. The way to make them white again is to cover them with 30% hydrogen peroxide in a beaker and then add an equal volume of 20% sodium hydroxide. A vigorous reaction occurs, and this is best done in a hood. However, if in this way enough Teflon is lost for the magnet to show through, it is best to discard the stirring bar.

SMALL-SCALE REACTIONS UNDER PRESSURE

For many years this meant the use of sealed tubes, with all the bother and risks involved, except if a small-size autoclave with a small-enough glass liner was available. More recently, with improvements in glass technology, simpler solutions have appeared on the market, and three examples are shown in Fig. 29(a),[47] (b)[48] and (c).[49] Such tubes are available in sizes of between 50 and 350 ml total volume.

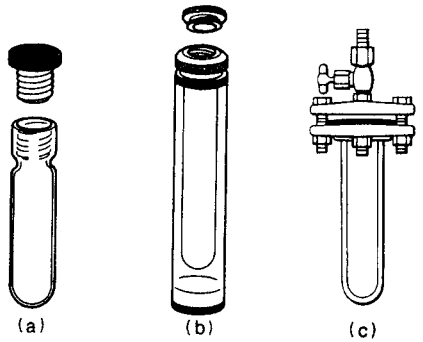


Fig. 29.

It is difficult, and indeed inadvisable, to give any guidance as to how much pressure any of these can withstand—so much depends on imperfections in the glass, which can include even outside scratches. What must be stressed are some basic safety precautions:

1. No such tube should ever be more than one third full.
2. While being heated in a liquid bath (never in a heating mantle!) *the entire length must be completely surrounded by a section of heavy iron piping* which is open at both ends so that the force of the explosion, if any, is directed up and down and never sideways.
3. No tube should ever be opened until the bath has completely cooled; and there should be additional cooling in case one of the products of the reaction has a vapour pressure higher than that of any of the initial components of the reaction mixture.
4. Before even starting you should look up the vapour pressure of the most volatile component of the mixture at the temperature to which the tube will be heated, so that you know what you are up against.

5

Isolating and Purifying the Product

THE WORKING-UP PROCESS

Capillary Pipettes

Earlier, stress was laid on choosing a reaction flask of a size appropriate not only for conducting a small-scale reaction safely but also for doing the working-up at the end. The indispensable tool for this is the capillary pipette. This will mean that except in very special circumstances, a separating funnel is an item which you can put into storage.

Such pipettes can be straight [Fig. 1(a)] or curved to get into awkward corners [Fig. 1(b)] or really contorted (e.g. for getting the contents out of a Kugelrohr bulb) [Fig. 1(c)]. Their basic use in the working-up process is as illustrated in Fig. 2 (here illustrating the advantage of using an extraction solvent heavier than water; see below). Two such pipettes can serve for really small-scale filtration (for example, into a flask sitting on a steam-bath prior to recrystallisation) (Fig. 3).

The adjective 'disposable' with which such pipettes (and a good many other items!) are sold need not concern you. Immediately after use each pipette should be placed (with the thin end up) in a chromic acid cleaning bath—for this a polypropylene 500 ml measuring cylinder will do very nicely. Here the

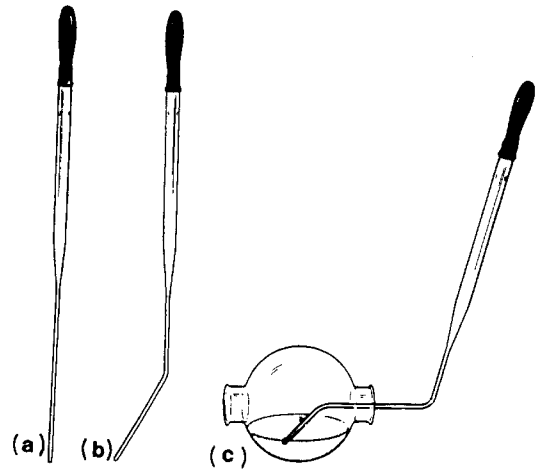


Fig. 1.

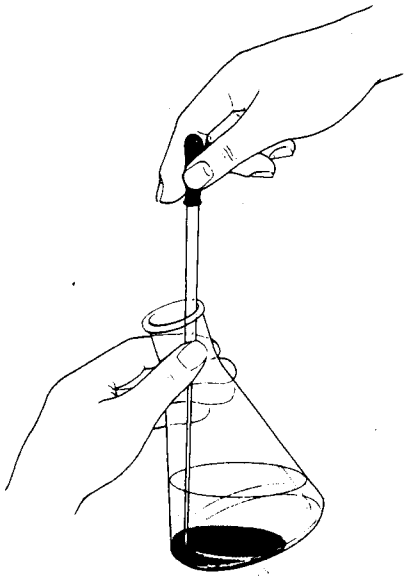


Fig. 2.

Fig. 3.

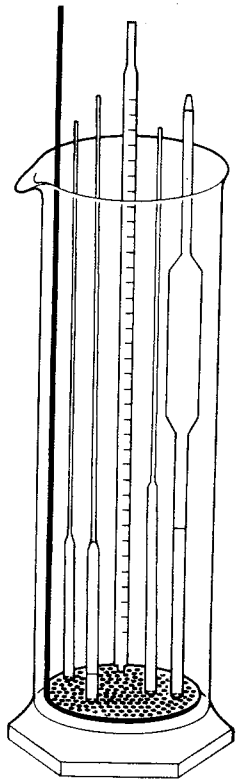


Fig. 4.

pipettes rest on a round PVC disk perforated with small holes for drainage, which can be lifted by an attached PVC stem (Fig. 4). When all the cleaning solution has drained down it is no trouble to take them out with tweezers and wash and dry them for re-use.

Some Basic Caveats and Rules

It is in the working-up process where probably the greatest number of avoidable mistakes are made by the beginning

researcher. The reason is not only the half-hearted if not sloppy way the topic is taught to the beginning student but also the manner it is airily glossed over in the literature by standard phrases such as 'the customary working-up ...', 'isolation by extraction (or trituration) ...' or 'chromatography of the crude product gave ...'. Another case in point is 'the mixture was poured into water'.

You should always approach with scepticism anything written in an Experimental section about the final state of a reaction, more often than not by someone who did not do the work himself. For instance, how often does one encounter the above sentence in connection with a Friedel–Crafts reaction or Claisen-type condensation, only to find that this is ludicrously impossible to carry out.

Rule Number One

Whenever a reaction set-up is disconnected for working-up, the first thing to do is remove grease from joints. This is best done by wiping them several times with tissue paper lightly soaked in carbon tetrachloride; for narrow openings a pair of tweezers should be employed. It is difficult to overemphasise this point; no extraction solvent should ever be added before this is done. Silicone grease has many advantages over other types but it has a pernicious habit of creeping into one's product unless removed first thing, as witness the characteristic broad band at 1050–1100 cm^{-1} in the infrared spectrum of so many beginners' preparations. It may also find its way into the glassware itself, a point which experienced glassblowers faced with a repair job never tire of making.

Rule Number Two

Before extraction, water-soluble solvents used in the reaction must be removed at the rotary evaporator. This most frequently means tetrahydrofuran, less so methanol or ethanol. Adding some water (and acidification if needed) beforehand will expedite this, particularly if the crude product can be induced to crystallise by seeding at some stage.

This is the proper occasion for a dire warning: *never ever leave the evaporation process unattended!* The chances are that at some stage a change in surface tension will lead to sudden foaming and resulting loss of product. The only thing that can possibly avoid this is to immerse the flask as deeply as possible in the water-bath.

With high-boiling solvents such as ethylene glycol, dimethylformamide or dimethyl sulphoxide, prior removal is not easy, but it often pays to get rid of as much as possible in a high vacuum.

Using the Right Extraction Solvent

This is no problem when the product's properties are known, but that is not so in most cases and it may be advisable to make some tests first on a micro-scale. The fact that it may separate as an oil does not mean that a convenient low-boiling but mediocre solvent such as diethyl ether can confidently be used. All too often it is on adding this that at least part of the product may crystallise out and cannot be redissolved. In such a case there is at least the added advantage of working-up in the reaction flask that you can remove such a solvent at the rotary evaporator and then try another one.

If at all possible solvents heavier than water should be used for extraction, such as dichloromethane or chloroform. One good reason is evident from Fig. 2. Another is economy. It is an instructive demonstration for any beginner to show him two conical separating funnels or round-bottomed flasks, each containing 100 ml of water, and then add 50 ml of diethyl ether to one and 50 ml of chloroform to the other. Further, the dissolving power of such solvents for difficult products (such as dicarboxylic acids and other polyfunctional compounds) can increase dramatically on adding up to 10% of tetrahydrofuran. This 'synergistic' phenomenon is not uncommon; mixtures of solvents (diethyl ether–benzene, chloroform–ethyl acetate) are

often better than the sum of their constituents. When using such mixtures one must naturally ensure that the mixture is definitely either heavier or lighter than water.

Taking a thin-layer chromatogram of the crude product at as early a stage as possible is advisable, because this can give a good indication not only of what happened in the reaction but also what the first purification steps should be. Moreover, while this is running you can get on with the working-up process itself. To facilitate this you should get into the habit of using an amount of solvent (having found the right one) to give a standard concentration of product. For example, 10% (w/v) is just right for a 1λ (μl) micropipette and the average silica TLC plate, 5% for one of 2 μl capacity, and so forth. There is obviously no problem in taking a sample when the extraction solvent is on top. If a solvent heavier than water is used then the sample can still be taken by drawing up a small amount in the capillary pipette and then applying a drop to the cleaned and drained micropipette—that is enough to fill it.

The amount of water used should be minimal but must take into account the solubility of inorganic salts finally present. For example, when sodium dihydrogenphosphate is used for acidification of a reaction mixture, the salts produced have a low solubility particularly when lithium ion is present, and this must be thought of in advance.

Further extractions and washings are best done using a consecutive series of Erlenmeyer flasks. And never ever throw the last layer away until you are sure that you have the entire product! You may find that you have some salting-out to do to extract the total product: use sodium chloride with neutral and basic solutions and ammonium sulphate for acidic solutions.

Snags Frequently Encountered

Some Carboxylic Acids and Enols May Form Insoluble Salts

When this is discovered (often too late), it can be disastrous for a systematic and quantitative working-up process, more so

because the resulting mess is often difficult to filter. When this type of product is expected it is best to make a preliminary micro-scale test. The solution of the problem, if there is any, lies in a change in cation (from sodium to potassium or lithium and occasionally ammonium). If this is of no avail it will be best to separate the bulk of the polar material from the total crude by crystallisation and then doing a proper work-up on the mother liquor.

The Acidic or Enolic Product is not Extracted Sufficiently by Alkali

This happens with tertiary and hindered carboxylic acids and with hindered phenols. The solution lies in lowering the polarity of the organic phase, e.g. by substituting benzene or toluene for diethyl ether, or adding hexane as much as possible without causing oiling-out of product. The same principle obviously applies to extraction of a weakly basic amine with mineral acid, where incidentally another phenomenon must be taken into account: salts of many higher molecular weight amines can be appreciably soluble in non-polar solvents.

Aqueous Alkaline Solutions of Organic Acids (or Acidic Solutions of Organic Bases) Tend to Dissolve Neutral Organic Material

Such solutions should be back-extracted at least twice to be on the safe side, and the extracts added to the neutral portions.

Emulsions

This common problem can be associated with any one or more of the above. The trouble is that every case is different. What should be tried are: (a) filtration of the whole under *moderate* suction through a reasonably wide bed of Celite or Filtercel—the culprit may be a minute amount of amorphous solid from an impurity in one of the reagents; (b) cautiously dissolving a neutral electrolyte (NaCl, Na_2SO_4) in the aqueous

phase; (c) adding a more polar solvent (diethyl ether, ethyl acetate or even some methanol) to the organic phase; and (d) most important of all, patience and waiting.

The Layer Boundary Cannot be Seen

This of course can happen with very messy and dark reaction products. Here each portion of extract must be carefully examined in the capillary pipette against a strong light, which may take a long time. Sometimes the problem can be solved by deliberately adding a white inert solid which will float at the boundary!

Dealing with the Extract

Solvents such as diethyl ether and ethyl acetate are never dried completely by either sodium sulphate or magnesium sulphate. Extracts in these solvents should be given a final wash with saturated sodium chloride solution, in order to reduce the amount of water still further, dried and then, before final solvent removal, a higher boiling or azeotroping solvent should be added. For this carbon tetrachloride is best, particularly when, as is usually the case, the crude product is to be examined by infrared or NMR spectroscopy.

Filtration of the dried product solution should be into a flask with an opaque and not clear (KPV) ground joint. Complete transfer of product by washing through with solvent is clearly shown up on this by allowing a drop of filtrate to evaporate on it. Even a trace of product can be seen in this way. This is also the case when using polypropylene instead of glass funnels; besides, their light weight will help to prevent toppling-over of the flask.

This is the stage at which some preliminary purification could be considered, in case the TLC examination of the crude reaction product indicates a highly polar and most likely highly coloured impurity. The first thing to try is to pass the dried extract through a short column of a neutral adsorbent such as

Table 1. Solubility of inorganic salts in organic solvents—comparative data (weight loss per hour on Soxhlet extraction with refluxing solvent)*

Salt†	Methanol	96% Ethanol	Abs. ethanol	Acetone	Ethyl acetate
Na_2CO_3	0.3 g	10 mg	4 mg	0	0
$NaHCO_3$	0.8 g	15 mg	15 mg	0	0
K_2CO_3	4.3 g	50 mg	50 mg	0	0
Na_2SO_4	5 mg	0	0	0	0
K_2SO_4	0	0	0	0	0
NaCl	1.2 g	0.15 g	70 mg	0	0
KCl	0.7 g	0.1 g	70 mg	0	0
NaBr	vs	ca 7 g		30 mg	0
NaI	vs	vs	vs	vs	2.3 g
KI	vs	vs	vs	3.3 g	10 mg
KNO_3	0.35 g	0.2 g	50 mg	9–12 mg	0
$KClO_3$	0.17 g	70 mg	30 mg	6–11 mg	0
$KClO_4$	0.2 g	70 mg	40 mg	0.25 g	6 mg
NH_4Cl	s	0.5 g	1.9 g	0	0
H_3BO_3	vs	vs	vs	ca 2 g	0.1–0.2 g

*vs, Very soluble; s, soluble.
†No weight loss of any of above with benzene, light petroleum, carbon tetrachloride, carbon disulphide, chloroform or diethyl ether (except with the last: H_3BO_3, 0.15 g).

Florisil. The amount of the latter should be about the same in weight as that of the product, and once the extract has passed through the column further washing should be effected with a more polar solvent, until later washings, evaporated separately, are shown to contain little or no product. Another action to consider is Kugelrohr distillation (see Chapter 8, p. 200).

If the product is highly water-soluble, then the only options open are either continuous extraction, or complete evaporation followed by extraction of the residue with an organic solvent. The former means having to find an apparatus that 'happens' to be of the right size for the volume of solution to be extracted, and for that either you have to be just lucky, or else it means further concentration or dilution. As for the second possibility, it is not generally realised that many inorganic salts can be appreciably soluble in some organic solvents; Table 1, based on data found in the literature,[50] gives some semi-quantitative and comparable figures to enable you to choose the appropriate solvent.

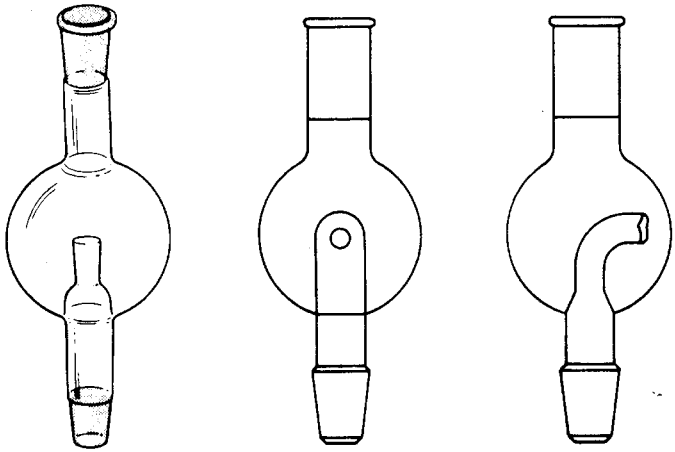


Fig. 5.

Solvent Removal

The rotatory evaporator has by now become an indispensable item of equipment. Together with the apparatus itself, the manufacturer will probably supply a mongrel-shaped flask which you are invited to use for all your evaporations large and small. One day you will no doubt find some use for it. What he does not usually supply, and what you really need, is a suitable adapter to guard against splashing and sudden ebullition leading to loss and contamination of both your product and of the apparatus. Suitable adapters are shown in Fig. 5(a) and (b). The latter will almost completely prevent contamination of the apparatus but, unlike the former, it will be more difficult to return solution back into the flask unless a curved capillary pipette is used. Such return is naturally almost impossible in another version where the tube inside the bulb is bent [Fig. 5(c)].

THIN-LAYER CHROMATOGRAPHY

Today's young researcher finds it difficult to grasp that there was a time when this technique just did not exist. Yes, chemists did somehow manage without it, they did find out somehow if anything happened in a reaction and how many products were formed, etc. It was a lot more difficult then, but then they worked a lot harder in those days!

Unfortunately, books on the subject still either cater for the advanced technician working in a specific field of compounds of mainly commercial and pharmaceutical interest (hence the subdivision into topics such as 'essential oils', 'alkaloids', 'lipids' and 'medicinal substances', (?!) or else go deeply into the theoretical side which will not in most cases help you with synthetic work.

The Tools

You had best cut your own plates. For that you need a good

glass cutter, not necessarily a diamond one. The type with small cutting wheels (usually six in a circle) needs to be grasped at the right angle. Some people never get the hang of it—if you are one of those, let a colleague do it for you.

The commercially available 20×20 cm plates (silica or alumina with a fluorescent material added) should be cut into two unequal halves, one 9 cm and the other 11 cm wide. Each half is then scratched at 15–25 mm intervals but the individual plates are not already broken off to begin with because you cannot foretell what total width of plate you will require in each case in the future. A 15 mm wide plate can accommodate two spottings and one of 25 mm is good for four spottings, whereas in examination of fractions from column chromatography you will need room for eight or even more and thus a plate 50–70 mm wide will be required. *Important*: For cutting the plates should be placed, with the uncoated side up, on a large sheet of filter paper. Any other type of paper, especially with print on it, may 'transfer' chemicals with which it has been treated, with disastrous consequences.

The 11 cm high plates are for more accurate work and where multiple development (see below) is to be used; the shorter ones are for routine work, e.g. with mixtures of substances of more widely differing polarity such as in fractions from column chromatography.

The above remarks apply to the more commonly used glass plates. With plates on a flexible base it probably pays to obtain the ready-cut microscope slide-sized ones, because cutting up larger sizes by yourself with a pair of scissors can create problems (crumbly edges and hence uneven ascent of the solvent front).

Alumina plates are more sensitive than silica plates to crumbling, mechanical damage and deterioration from the atmosphere in the course of time; hence it is best not to cut down more of the larger plates than are needed in the immediate future.

For spotting, the commercially available micropipettes, of 1, 2 or 5 λ size should be used, because uniformity in spotting is

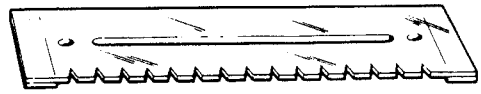


Fig. 6.

very important and you can never achieve this by relying on home-made capillaries. These micropipettes are another item sold as 'disposable' whereas in fact they are not. With one or two applications of a drop of solvent, followed by drainage on a filter paper, they are as good as new, at least until they become clogged.

An old ruler, notched at regular (say 6 mm) intervals and provided at each end with 2 mm thick support spacers (see Fig. 6) should do nicely as a spotting template. The long notch along the centre is for preparative plates (see below).

Development jars are best if they have a narrow rectangular shape. Most of the commercially available ones are too large and moreover made of pressed glass and thus not sufficiently transparent (a matter of importance with alumina plates, on which it is not easy to follow ascent of the solvent front). Hence one has to fall back on using either tall, narrow, spoutless beakers (Berzelius type) or suitable household jam, jelly or preserve jars. They must have as flat a bottom and as wide an opening as possible. Perhaps next time at the supermarket you should gently steer whoever is in charge of the shopping towards those brands which will meet with these requirements; and do not forget to take a tape measure with you. Any such vessel must have a uniform rim for covering with a watch-glass or Petri dish.

Development of the Plate

The development vessel must be kept saturated with solvent vapour at all times. This can be ensured by lining at least on one side with a strip of filter paper and shaking the whole frequently (not, of course, while a side is being developed!).

The best elution solvent combination is a pair mutually mis-