

Aldrichimica Acta

Volume 10, Number 1, 1977



Dedicated to Professor Robert Burns Woodward on his sixtieth birthday.

Aldrichimica Acta



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A publication of ALDRICH CHEMICAL COMPANY, INC.

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We at Aldrich are happy to dedicate this issue of the Aldrichimica Acta to Professor Robert Burns Woodward on the occasion of his sixtieth birthday.

Professor Woodward is one of the greatest living chemists. His name conjures visions of synthetic jewels and symmetry rules, of noble prose and Nobel Prize. Before his time, the world's greatest chemists were German, English and Swiss. Through his accomplishments, example and teaching, we now have great schools of chemistry in America.

May we say what the Bible says of the greatest lawgiver: Let his eyes not be dim nor his natural strength abated — from 60 to 120.

About Our Cover:

Our chemist-collector, who has known and admired Professor Woodward since 1947, had the pleasant problem of choosing that painting in his collection most fitting for the cover of the Acta dedicated to Professor Woodward. We were not surprised that he picked this *trompe l'oeil*, once in the collection of the King of Saxony and painted by a late seventeenth century Bolognese artist, for the analogy is clear. The painting depicts the marriage of King Alexander the Great and Princess Roxana, and thus the meeting of the greatest cultures — Greek and Persian — of their time. So we find in Professor Woodward the junction of the greatest sciences of our time — chemistry and the life sciences.

Are you interested in our Acta covers? *Selections from the Bader Collection*, with 30 duotone reproductions, many of previous Acta covers, and an introduction by the late Professor Wolfgang Stechow is now available to all chemist art-lovers.

Many of the early issues of the *Aldrichimica Acta* have become very rare. Please do not throw your issues away. In time, we believe that complete sets will become valuable, and — if you do not want to keep them — there probably are chemists near you who would be interested.

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Lab Notes

Few reactions in organic synthesis are as useful as the Wittig condensation. Often, however, high-purity intermediate alkyl triphenylphosphonium halides are essential for high and reproducible yields. We have developed a very general method for recrystallizing these compounds. In all cases we have experienced, the yield of the subsequent Wittig reaction has been improved by this purification.

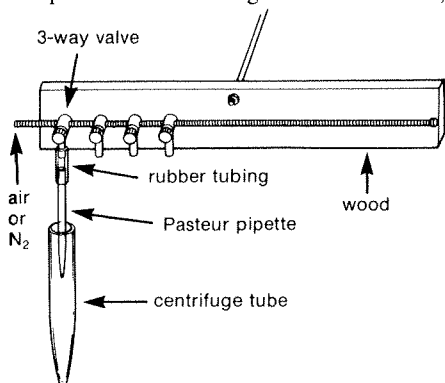
The impure phosphonium salt is dissolved in the minimum of methylene chloride (n ml). This solution is diluted with methylene chloride (n ml), then tetrahydrofuran (n ml). The resulting mixture is then concentrated to a volume of n to $2n$ ml, then cooled. The resulting crystalline material is pure phosphonium salt. Weight recovery is excellent.

This method has been applied to the purification of a wide range of both mono- and bis-phosphonium salts, and is suitable, with appropriate precautions, to the preparation of analytical samples.

Nicholas Darby, Ph.D.
Edmonton, Alberta
Canada T6C 4A9

We find the following evaporator effective and inexpensive for reducing solvent volume of sample extracts, such as urine and drug extracts, for thin layer chromatography and gas liquid chromatography.

The unit consists of one or more 3-way fish-aquarium valves connected in series and mounted on a "T" fashioned from a strip of wood and a length of threaded rod,



which can then be mounted on a ring-stand. A disposable Pasteur pipette is attached to the appropriate prong of the valve to direct the flow of air or nitrogen for evaporation of solvent in a 15-ml con-

ical bottom centrifuge tube. The rack of tubes can be placed in a water bath to promote evaporation.

Glenn Murphy, Chief Chemist
Toxicology Laboratory
Bureau for Health Services
Frankfort, Kentucky 40601

A very nice and inexpensive introduction chamber for a glove bag can be made from an empty coffee can and two pieces of copper tubing. This chamber obviates the need for evacuating and refilling the bag each time a sample is to be introduced into or removed from the bag.

The apparatus consists of a coffee can with both the metal ends cut off and replaced with the plastic caps which are provided for resealing the opened cans. Two holes are then drilled in the seam along the side of the can where it is soldered together. The two copper tubes are then soldered into these holes. To these tubes are attached a vacuum line and an inert gas line. The completed chamber can then be inserted into the opening of the glove bag, which is sealed to it by means of rubber bands.

There are two methods for flushing air from the antechamber: gas can be bled in and out simultaneously, or the can can be repeatedly pumped down and refilled. Most cans (and especially the smaller ones with low cap area) will take a respectable vacuum, and this can be improved by cementing hard plastic discs onto the outside of the plastic caps, which will help keep them from bowing inward too much.

Edward C. Greer
11 Old West, U.N.C.
Chapel Hill, N.C. 27514

When separating an organic phase from an aqueous phase, it is often difficult to distinguish one from the other on cursory examination. It often becomes necessary to consult tables of specific gravity or to carry out some other simple, but time-consuming investigation which interrupts the flow of the experiment.

I find that the following quick test produces the correct answer in most cases. A drop of each phase is placed on the edge of a piece of filter paper. Upon attempting to tear the filter paper, you will find that the aqueous spot tears without effort and the organic spot resists tearing.

Paul R. Horinka
Research Chemist
American Color and Chemical Corp.
Reading, Pa. 19603

In solution preparation in test tubes or flasks, one is faced occasionally with the problem of entrapped air, microbubbles or foam making it difficult to ascertain

whether dissolution is complete. Since most labs now have ultrasonic cleaning baths, immersion of the tube or flask in the bath for one second, causes an instantaneous clearing of the solution for complete visibility.

A.C. Megalos
Senior Scientist
Technicon Instruments Corporation
Tarrytown, New York 10591

A large test tube mounted vertically with its mouth up and slightly below the surface of a stirred water bath will do an amazing job of collecting the dirt and debris that otherwise soon make such a bath murky.

R. Keith Osterheld
Professor
University of Montana
Missoula, Montana 59801

Any interesting shortcut or laboratory hint you'd like to share with ACTA readers? Send it to Aldrich (attn: Lab Notes) and if we publish it, you will receive a handsome red and white ceramic Aldrich coffee mug as well as a copy of **Selections from the Bader Collection** (see "About Our Cover"). We reserve the right to retain all entries for consideration for future publication.

"Please Bother Us."

by
R. Bader

By a happy coincidence, the very first telephone call I received after our advertisement "Please Bother Us" appeared in *C & E News*, was from Professor R.B. Woodward at Harvard, who was looking for an out-of-the-way quinone, 2,5-dihydroxybenzoquinone. We have over three hundred quinones in our Library of Rare Chemicals; this one was among them, so we mailed 5g to Professor Woodward that day. Also, we decided to list it in our catalog-handbook, and now have several kilos in stock for immediate shipment.

It was no bother at all, just a pleasure to be able to help.

Robert Burns Woodward: Three Score Years and Then?

David Dolphin
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Synthetic organic chemistry began 150 years ago when, in 1828, Wöhler¹ prepared urea from ammonium cyanate. "The unexpected result," reported Wöhler, "is also a remarkable fact inasmuch as it presents an example of the artificial production of an organic, and so-called animal, substance from an inorganic substance." Liebig, who at this time was working in similar areas, initially doubted Wöhler's work but was soon convinced, however, of its correctness, and the two young chemists became close and lifelong friends. Only a decade after Wöhler's original discovery, he and Liebig, writing jointly on uric acid, asserted that, "The philosophy of chemistry will draw the conclusion that the synthesis of all organic compounds, as long as they are not a part of an organism, must be seen as not merely probable but certain."² No one has more completely fulfilled this prophecy than R.B. Woodward, who in 1965 was awarded the Nobel Prize for art in organic synthesis. Some of his most notable achievements are the synthesis of vitamin B₁₂, the most complex non-polymeric naturally occurring substance, as well as a series of other synthetic triumphs which have each in their turn established standards of elegance and creativity for which most other organic chemists can only hope to strive.

How does one tell the chemical community anything about Woodward which either they do not already know, or which they cannot readily learn by consulting any of the numerous collections of biographical data? I could list here the more than 30 honorary degrees which have been bestowed on him, and which are recorded in a closet in Cambridge as an array of multi-

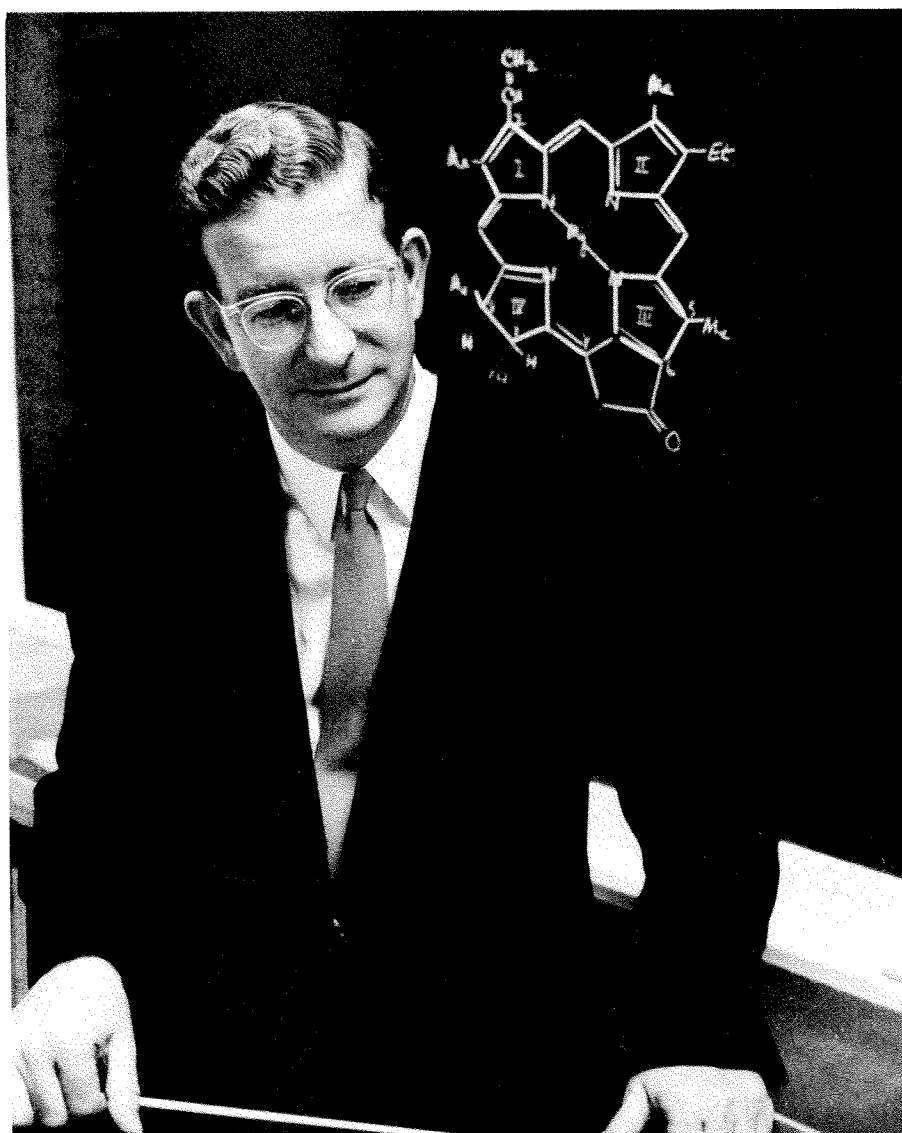


Fig. 1. Plan in detail, then carry it out (printed with permission of the American Chemical Society, from *Chemical and Engineering News*, Nov. 1965, p. 38).

hued academic robes (with the exception of one from a Scottish University, which shall remain unnamed, which insisted that if Woodward wanted the gown, he would have to buy it!). And I could follow this by a list of awards which would include the Theodore William Richards Medal, the Roger Adams Award, the Willard Gibbs Medal, the Pius XI Gold Medal, the National Medal of Science, the Nobel Prize in Chemistry, the Lavoisier Medal, the Decorated Order of the Rising Sun (Japan), and on into a list which would require more space for its completion than the *Aldrichimica Acta* has available. Rather than pursue this typical approach, I have decided to take a light-hearted look at the man as well as his chemistry.³

Neither teacher nor student of chemistry can have failed to have come across many of the contributions that R.B. Woodward has made to science in the past four decades. This was certainly true for me as an undergraduate, as well as a graduate of chemistry at the University of Nottingham where I worked with Alan Johnson in the early 60's. When it became clear that I would probably obtain my Ph.D., I asked my mentor what he would suggest I do after I was through at Nottingham, and he advised me that it might be good for my soul to go somewhere where I would be expected to work a little harder than I had been used to, and that I might think about trying to work with Woodward at Harvard. After some considerable agonizing I came to the conclusion that surely all of the rumors I had heard about this man, his work habits and those of his collaborators, could not possibly be true, and that I should indeed see if Woodward would give me a postdoctoral appointment in his laboratories. Having prepared a carefully worded letter I took it along to Alan Johnson to see if it met with his approval, and I was told I would be wasting my time if I sent it since Woodward never replied to letters. I have since learned that this was a slight exaggeration; nonetheless, the letter was never sent. Instead, however, when a few days later I was present at a half-day symposium on Vitamin B₁₂ in London at the Royal Society, during one of the traditional tea breaks I was approached by an individual whom I knew, by the tell-tale cigarette and blue tie, could be none other than Woodward. Within ten seconds he ascertained that I did indeed wish to work with him, and suggested that I should write to his secretary and say that I would be arriving the following September.

Having made plans to cross the Atlantic in search of fame and fortune, I thought it advisable to familiarize myself in a general way with some of Woodward's work, and



Fig. 2. RBW working with fibrous proteins (from the *Boston Herald*, Wednesday, June 18, 1947).

am sure that you will be as interested as I was to note that his first two papers were:

Precipitation of barium in the copper-tin group of qualitative analysis, W.J. Hall and R.B. Woodward, *Ind. Eng. Chem., Anal. Ed.*, 6, 478 (1934).

The staling of coffee II, S.C. Prescott, R.L. Emerson, R.B. Woodward, and R. Heggie, *Food Research*, 2, 165 (1937).

But a glimpse of the greatness to come was evident in his third contribution to science:

A pressure regulator for vacuum distillation, R.L. Emerson and R.B. Woodward, *Ind. Eng. Chem., Anal. Ed.*, 9, 347 (1937).

Arriving in Boston in the fall of 1965, I was met by his secretary, Dodie Dyer, and told if I would like to wait in the library Dr. Woodward would soon see me. And indeed, two weeks later, I was shown into his office, where we discussed what I might do during my stay at Harvard and agreed that I would participate in the synthesis of B₁₂. Having established my scientific program for the period of my stay I turned my attention to more important matters such as the length of any holidays that I could expect. After a brief pause Woodward shrugged his shoulders and said, "Well, I take Christmas Day off."

During this first discussion I had been seated at the side of his desk. Convinced, as I am now, that Bob Woodward does nothing which he has not carefully thought out I have realized since that the small

quotation I saw then in front of him was as much for the benefit of his colleagues as for him, and after slowly moving my position so that I was able to read it, at the conclusion of the interview I saw the words that were to encourage me in my work for the next year: "Let sleeping dogs lie."

That year I spent in Woodward's laboratories was an especially exciting one and was highlighted early one morning when, as I walked into the laboratories, I heard the clinking of champagne glasses, and realized that although I had missed the news, the inevitable had obviously happened. The speed at which the champagne appeared in Bob's office surprised me, but I soon found out that, in fact, the champagne had been laid down by the department some time earlier in anticipation of the Nobel Prize. As the party progressed it was generally felt that signed champagne bottles would make a suitable memento of the occasion; however, it transpired that there were more drinkers than bottles. Woodward soon remedied this problem by holding sufficient parties until enough bottles had been accumulated. A few days later the Swedish television company came into Bob's laboratories and said how disappointed they were that they had missed the party, since they felt that scenes of a less formal nature might be suitable for a program they were preparing on that year's Nobel Laureate. Not wishing to disappoint his visitors from Sweden, Bob threw another round of parties which were received by his group with no less enthusiasm

than the initial ones.

Since he obtained the highest accolade in his field it might be of interest to see how Woodward's career had developed up to the time of the Nobel Prize. Born on April 10, 1917 in Boston, Woodward spent his childhood in a suburb of that city, Quincy. To give you a brief glimpse of his childhood I quote from an article in the Boston Daily Globe of June 8, 1937. "As a boy in short pants in Quincy Grammar School, he consistently brought home report cards dimmed with a pair of D's for conduct and effort. The Woodward youngster, who was always playing in the cellar with a chemistry set, received three double promotions hurdling the fourth, seventh and tenth grades, all the while whispering in classes, chewing bubble gum, being the last one in after recess and pulling little girls' long curls." I can assure you, after ten years of close association with Bob Woodward, that things have certainly changed since his earlier days — I don't think I have seen him blowing bubble gum in a long while.

In addition, it would appear that the passing years have also instilled a little caution. Recently, at an MIT fraternity house Pat⁴ introduced RBW to a striking young redhead who was interested in meeting him. Amid the din and accompanying revelry the two remained locked in an animated conversation. After some time RB, looking a little disillusioned, came over and said: "I find this young lady quite interesting. However, she has just made a strategic mistake." "What could she have done?" Pat queried. "Well," said RB, "she

just told me that she had been engaged to a professional wrestler. And, Pat, that is a very hard act to follow."

Returning to the report from the Boston Globe we find that "in 1933, a sixteen-year-old lad from Quincy with a very distinguished scholastic record appeared at MIT where professors, being only human, formed a quick but wrong impression of him. The savants at this institute solemnly soliloquized, 'Woodward as a freshman had much to learn. He was in no position to think the world his oyster in or out of season, so happy-go-lucky, not at all the grim and studious type.'" One professor had remarked, "Well, the Institute, young man, is a different place than a public school." It would appear then, as now, that MIT professors can be mistaken, for in four years Woodward had obtained his Ph.D. from MIT — not, however, without some difficulties. His transcript which shows a 4.9 out of a possible 5 was highlighted by a double F in gym.

Clearly Woodward's career at MIT was atypical in that he obtained both his Bachelor's and Doctorate degrees by the age of 20. Again quoting from the Boston Globe, "The achievement was the more remarkable in that Woodward obtained his goal after only four years of study against the seven usually required; when during this period much of his time had been devoted to outside work to finance his collegiate career."

"I never heard of it being done by any young man before, either at Tech or anywhere in the world," was the commendation of James Flack Norris, Professor of Organic Chemistry and Director of the Tech Research Laboratory in the field in which young Woodward took his degree.

While taking the regular freshman courses, during the first semester at the Institute, Woodward applied for a seat in the laboratory. The Organic Department told him that only graduate students, men who possess degrees, are allowed that privilege; but his appeal interested the Department and he was told that if he could supply a list of the experiments he was planning, he might be given some consideration. A few days later he produced a list of experiments that showed such outstanding originality and scope that he was granted a seat.

Toward the end of the second semester of his freshman year Woodward walked into the examination room where third-year students were being tested in organic chemistry. He inserted a note in his examination book, asking the professor to correct it, and if possible, to give him credit.

At the beginning of his second year he was given his own laboratory in which to experiment. In that year he happened to attend an organic chemistry lecture in which the professor told about the difficulty of synthesizing the female sex hormone from carbon. At the end of the lecture Woodward came to the professor and showed him a way which might lead to such a synthesis.

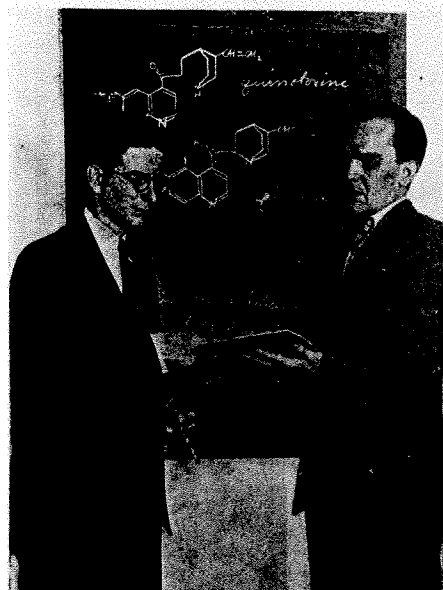
The professor was amazed; the entire organic chemistry department became excited. For Woodward had hit on something that might prove to be revolutionary in the field of organic chemistry.

During his third year Woodward took as many as 15 courses in one semester so that he might receive his Ph.D. sooner. The faculty permitted him to spend as little time as he wished in classes. Instead he studied the required subject matter independently and simply presented himself at the examinations. Again and again he walked off with honors in organic chemistry courses. At the end of his third year Woodward was notified that he was to be granted a bachelor's degree.

His last and fourth year at Tech, Woodward describes as his happiest, for he was able to spend his time in the research laboratory where he could resume his experiments, which he had begun in his second year at the Institute, on the female hormone. He did this work independently and wrote his thesis on it.

In explaining Tech's attitude toward Woodward, during that period of time, Professor Norris says, "We saw that we had in our midst a person who possessed a very unusual mind. We wanted to let it function at its best. If red tape, which was necessary for other less brilliant students, had to go, we cut it. We did for Woodward what we have done for no other student in our department, for we have had no student like him in our department. And we think he will make a name for himself in the scientific world." Norris further said, "But unlike some scholars, he will not burn out suddenly." It was not to be long before these prophesies were to be fulfilled.

Upon graduating from MIT Woodward spent the summer of 1937 at the University of Illinois but, with the approach of winter, migrated to warmer climes and moved back to Cambridge, where he became an assistant to Professor Elmer Peter Kohler at Harvard. The following year he was elected to the Harvard Society of Fellows, and by 1941 had published a series of papers on ultraviolet spectral structure correlations which are still used to this day. In 1944 Woodward (as a consultant for the Polaroid Corp.) and Bill Doering achieved



Robert B. Woodward and William E. Doering, set to synthesize quinine

Fig. 3. Printed with permission of the American Chemical Society, from *Chemical and Engineering News*, 1944, p. 730.

the total synthesis of quinine in only 14 months (Fig. 3). In 1947 he was to elucidate the structure of strychnine, to be followed in 1954 by total synthesis of strychnine and lysergic acid. The synthesis of strychnine was not without its difficulties, however, and after several months of trying to close the 6th ring, and after the most recent experiments had failed, Bob is recorded as saying, "If we can't make strychnine, we'll take strychnine!"

Prior to the total synthesis of strychnine both cholesterol and cortisone were synthesized, and in 1952 Woodward proposed the sandwich structure for ferrocene.

Few personal accounts of the major discoveries in chemistry are documented. An exception to this is the dream of August Kekulé⁵ which led to the suggestion that benzene contained a cyclic structure. "There I sat and wrote my Lehrbuch," reported Kekulé, "but it did not proceed well, my mind was elsewhere. I turned my chair to the fireplace and fell half asleep. Again the atoms gamboled before my eyes. Smaller groups this time kept modestly to the background. My mind's eye, trained by repeated visions of a similar kind, now distinguished larger formations of various shapes. Long rows, in many ways more densely joined; everything in movement, winding and turning like snakes. And look, what was that? One snake grabbed its own tail, and mockingly the shape whirled before my eyes. As if struck by lightning I woke; this time I again spent the rest of the night to work out the consequences."

This dream of 1865, occurred 35 years before Sigmund Freud's theories were published in 1900,⁶ and one can but wonder about Freud's reaction to snakes' biting their own tails! If, however, this led to the elucidation of the structure of benzene, what thoughts led Woodward to the sandwich structure of ferrocene would, I am certain, prove fascinating.

While the suggested structure for ferrocene initiated an era of organometallic chemistry, it also aided in the demise of Woodward's continuing practice at the bench. About 3 a.m. one day the group was gathered in the laboratory suggesting ways to try and oxidize or reduce the then-new ferrocene. RB put a lump of FeSO_4 into a separatory funnel and shook it with a solution of ferrocenium ion to reduce it. On being shaken, the funnel was broken by the lump, and the solution poured out onto RB's trousers (where it had the audacity to remain oxidized).

In 1960 Woodward announced the total synthesis of chlorophyll (Fig. 1), having already synthesized lanosterol and reserpine, and followed these successively with



Fig. 4. A telegram from Sweden!

syntheses of tetracycline, cortisone and cephalosporin during the period in which he was awarded the Nobel Prize (Fig. 4).

While I have chosen only a few of the highlights in the above list of achievements in synthesis, it must be remembered that the theoretical aspects of organic chemistry are areas to which Woodward has also turned his talents. The latest of these is the conservation of orbital symmetry developed by Woodward and Hoffmann in the late 60's, and so elegantly summed up by them in their *Angewandte Chemie* article in 1968 where, in considering violations to the rules, they concluded "there are none!" Oosterhoff had suggested that orbital symmetry might play a role in electrocyclic reactions, and, while introducing Roald Hoffmann to an audience, made the observation that throughout the history of organic chemistry a number of significant contributions had been made by various distinguished Hoffmanns, among them being August Wilhelm von Hoffmann, and Friedrich Hoffmann. However, Oosterhoff noted, "of all the Hoffmanns the most famous is undoubtedly the Hoffmann whose first name is Woodward."

The greatest of all of Woodward's synthetic achievements is that of Vitamin B_{12} , which, in collaboration with Albert Eschenmoser, was completed in the early 70's. As colloquia chairman at Harvard I persuaded Woodward to present a talk on the synthesis of B_{12} . Our colloquia at Harvard were normally of an hour duration, and at first Bob was reluctant to lecture, since he assured me that there would be no way he could say his piece in an hour. If we were to schedule the talk at 5 p.m. as nor-

mal, we might break into the dinner hour and upset the audience. We easily overcame these objections by starting the talk at 8 p.m. which of course left us the rest of the evening, and if necessary the following morning, for the remainder of the presentation. It had not gone unnoticed, on earlier occasions, that Woodward's talks had occupied several hours, and since I had no reason to expect that this occasion would be any different I felt it might be appropriate to give a more detailed than usual introduction of our speaker.

A few weeks earlier Duilio Arigoni had presented the Tishler lectureship to the department, and had been introduced by Woodward who took some delight in giving a detailed discussion of a horoscope that had been prepared for Arigoni. I remembered, too, that Woodward had told me several years earlier that one should use all available avenues to gain information about a subject. In particular I remember that Woodward was trying to repeat some of Thorpe's earlier work in which he had claimed to have synthesized some derivatives of tetrahedrane. By the time Woodward was attempting to repeat this work Thorpe had died and parts of the experimental details were no longer available. Woodward knew, however, that Lady Thorpe was a clairvoyant who claimed to be in touch quite regularly with her husband, so Bob thought that this might indeed be a unique way of obtaining information and would certainly constitute a novel footnote. It thus seemed appropriate to me that, in the absence of a clairvoyant, possibly a detailed analysis of a horoscope prepared for Woodward might be included in my own introduction. At the time of the

preparation of Arigoni's horoscope, it had been suggested by the young lady preparing the horoscope, that perhaps Bob himself might like to have a horoscope prepared, but that in order to do this she would need the exact time, to the minute, of Woodward's birth. Woodward suggested that rather than use that time, which he didn't know anyway, and doubted that it could now be found, the young lady should prepare a horoscope for every minute of the day of his birth, and then by looking at the various comments decide what time he was born. Since I had neither the time nor the resources to undertake this obvious scientific but rather lengthy procedure, I determined to try and establish the exact time of Woodward's birth. A trip to the Massachusetts State House told me that Woodward was born on April 10, 1917 in the Boston Lying In Hospital for Women, but unfortunately no time had been recorded. However, the Boston Lying In Hospital for Women is an old established hospital and they informed me that for a small research fee they would check their records and find the information I needed, and behold a few days later a letter (Fig. 5) appeared recording Woodward's time of birth as 3:39 a.m. This is an especially significant time I feel, for I remember, one morning toward the end of a party in Bob's apartment, we saw the sun rise over the river Charles at about four in the morning. Woodward commented that yes, indeed he observed this every morning. Somewhat to our amazement he told us that he slept only three hours a day and had done so for as long as he could remember, and that he usually went to bed about 1 a.m. and got up

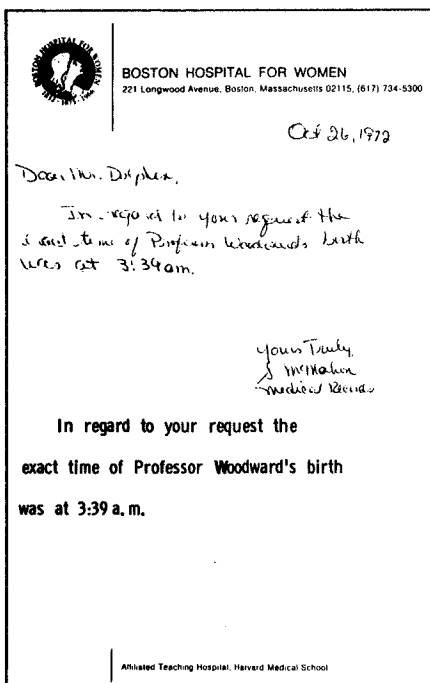


Fig. 5.

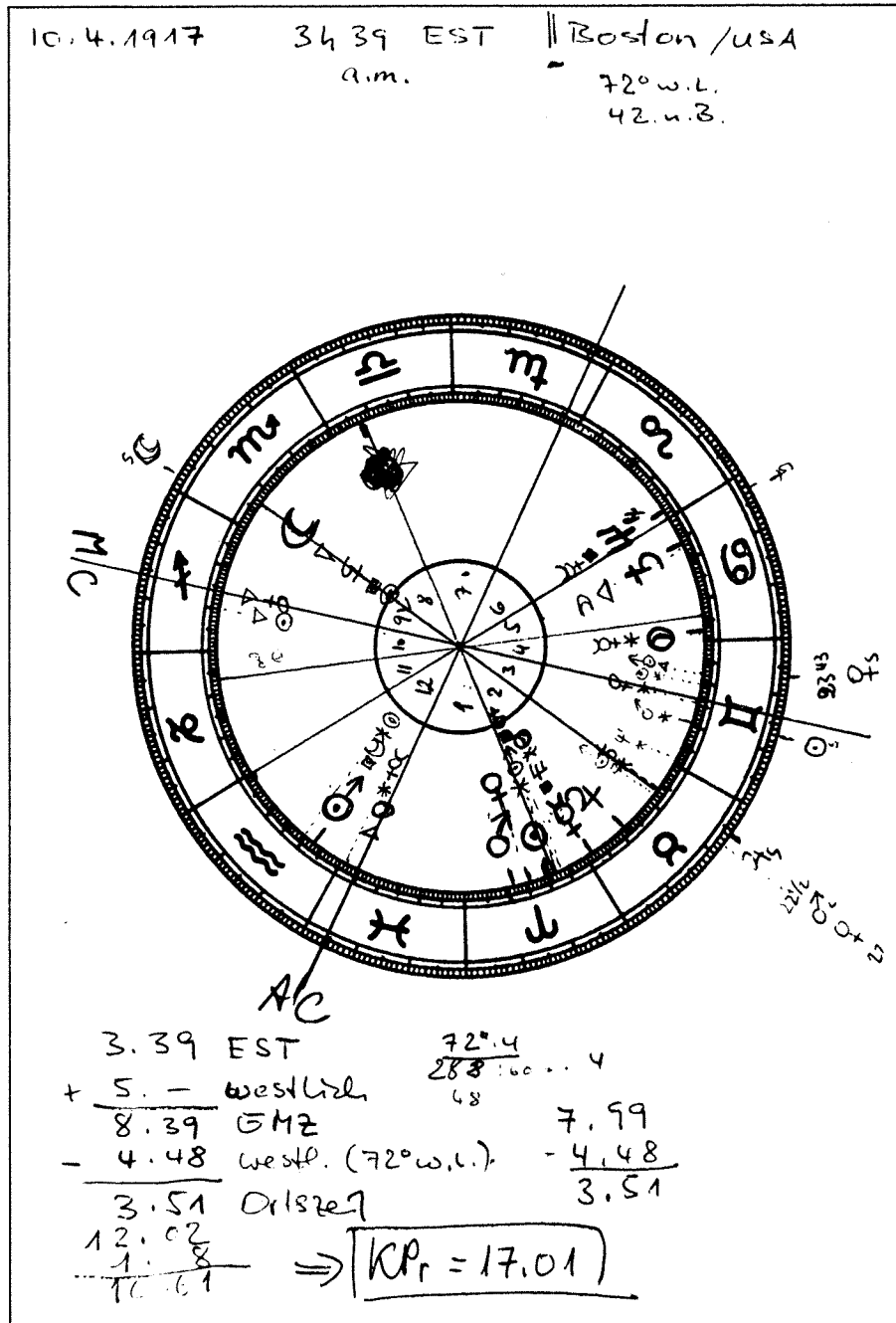


Fig. 6. Horoscope prepared for Woodward.

around 4 a.m. It would appear that he acquired this habit at a very young age then, and hasn't changed it since.

Having determined the exact time of Woodward's birth, I transmitted this information to Zürich and on the day of Woodward's lecture at Harvard, Arigoni flew in with the appropriate document and a somewhat detailed analysis of the horoscope. You will appreciate that it would be ignoble of me to outline here details of many of the comments that were made, but I reproduce in Fig. 6 the horoscope, so that those of you who are trained in the art of interpreting such documents can come to your own conclusions. I must make it clear right from the

beginning that up until that time I had little faith in horoscopes, but many of the interpretations were indeed accurate in many respects; we knew we were on to a good thing with the first comment — Woodward's favorite color was red! It was noted, however, that his career had begun at 22, an accurate deduction, and that the man for whom this horoscope had been prepared should be a scientist. And not only that, that he should be a chemist, too. I must admit that to this day I do not know how much of this information came from the horoscope and how much came via Arigoni. The analysis went on to point out the subject was a user of nicotine and liquor, but was such a strong individual that

these had no effect on his health. Woodward ran true to form to show us, that night, how accurate the statement was by consuming his usual number of packages of Benson & Hedges and by finishing the two pints of Daiquiri that had been prepared for him as part of my introduction. Despite what non-smokers believe, among them such crusaders as James the First, who had this to say —

Smoking is a custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black stinking fumes thereof nearest resembling the Stygian smoke of the pit that is bottomless.

— the habit has been a tradition amongst synthetic chemists since the time of Wöhler and Liebig, both of whom were heavy smokers, especially Wöhler, who once made this comforting comment to a non-smoking colleague: “there are examples of non-smokers who became bearable chemists; however, this occurs only rarely.”⁷

The horoscope indicated that the individual was forceful, energetic, had a good practical sense but was by no means diplomatic, and that he impressed others with his own personal viewpoint. And the individual was possessed with a phenomenal memory. To this I can personally attest. In late 1973 just before I left Harvard to move to the University of British Columbia, I was discussing the oxidizing power of oxaziridines with Woodward, who said that he recalled a paper from the Redstone Arsenal which he had read a while ago, where oxaziridines were titrated with iodide and hence oxidants. As a measure of Woodward's memory it transpires that the paper he referred to had been written about twenty years earlier, and that the iodide titrations were described in a footnote to the experimental section.

But let me return to Woodward's latest accomplishment. Although the total synthesis of B₁₂, in the form of cobyrinic acid, formally represented a total synthesis of the vitamin itself, it was only a year ago that the complete synthesis was achieved, when the nucleotide loop was attached to the cobyrinic acid. (Fig. 7)

My latest count of the people involved in this undertaking, in both Cambridge and Zürich, totalled about 100 postdoctoral fellows. It is, of course, apparent that during the past 40 years Woodward's achievements must also be gauged in reference to Woodward as a teacher. During these past four decades nearly 400 students have been

associated with him. It is said that a man can be judged by the company he keeps, and it is certainly true that a chemist can be measured by the men he has trained. It would be inappropriate to list here all 400 colleagues; other ventures being planned to celebrate Woodward's 60th birthday will better measure the magnitude of this group.⁸ I have however gone through the list of Woodward's collaborators and randomly selected about ten percent of the names:

Bill Ayer, Jerry Berson, Ray Bonnett, Rich Borch, Axsell Bothner-By, Ron Breslow, Bill Chan, Malcolm Clark, Gerhard Closs, Pat Confalone, Pierre Deslongchamps, Bill Doering, Paul Dowd, Ian Fleming, Chris Foote, David Ginsburg, Jacques Gosteli, Hans Gschwend, James Hendrickson, Ken-ichi Hiroi, Ken Houk, Shô Itô, Bill Jencks, Tom Katz, Andy Kende, Yoshi Kishi, Hoshiro Kobayashi, Jean-Marie Lehn, Willy Leimgruber, David Lemal, Paul de Mayo, Jerry Meinwald, David Ollis, Roy Olofson, Avram Patchornik, Subramania Ranganathan, Myron Rosenblum, Dick Schlessinger, Franz Sondheimer, Bal Dattaraya Tilak, Denny Valenta, Harry Wasserman, Larry Weiler, Ernie Wenkert, Emil White, Mark Whiting, Alex Wick, Charles Wiesner, Reuven Wolovsky, Peter Yates, Alexander Gregoryevitch Yurlchenko, Howie Zimmerman.

It is inevitable, in preparing a list of this type, that some of the more famous colleagues should have been left out. These names I have added below.⁹

In May of 1944 *The Tech* (The MIT newspaper) made the following comment. “Professors who have known him well have stated that Woodward was excellent not only in *chemical* subjects but in *academic* studies as well.” Those same professors would now have to admit that through the efforts of Robert Burns Woodward chemistry can at last be acclaimed a scholarly and academic pursuit.

And what of the future? You might imagine that the best answer to this question would come from the oracle himself. However, such pilgrimages are usually destined to failure. For example, I remember a press conference that was held on the morning that Bob won the Nobel Prize. A reporter from one of the local newspapers asked if he thought that he now would begin to synthesize life in the test tube. After a moment's reflection he looked up and said, “No, I am quite happy with the way it is done now.”

After all of Woodward's scientific achievements one might imagine that there is nothing that he can do to exceed, for instance, the elegance or complexity of the B₁₂ synthesis. I am certain that this is not so, and that we shall see even greater triumphs in the future. If you doubt this statement I leave you with the words of Lewis Carroll:

“There is no use trying,” she said; “one can't believe impossible things.” “I dare say you haven't had much practice,” said the Queen. “When I was your age, I always did it for half an hour a day. Why, sometimes I believed as many as six impossible things before breakfast.”

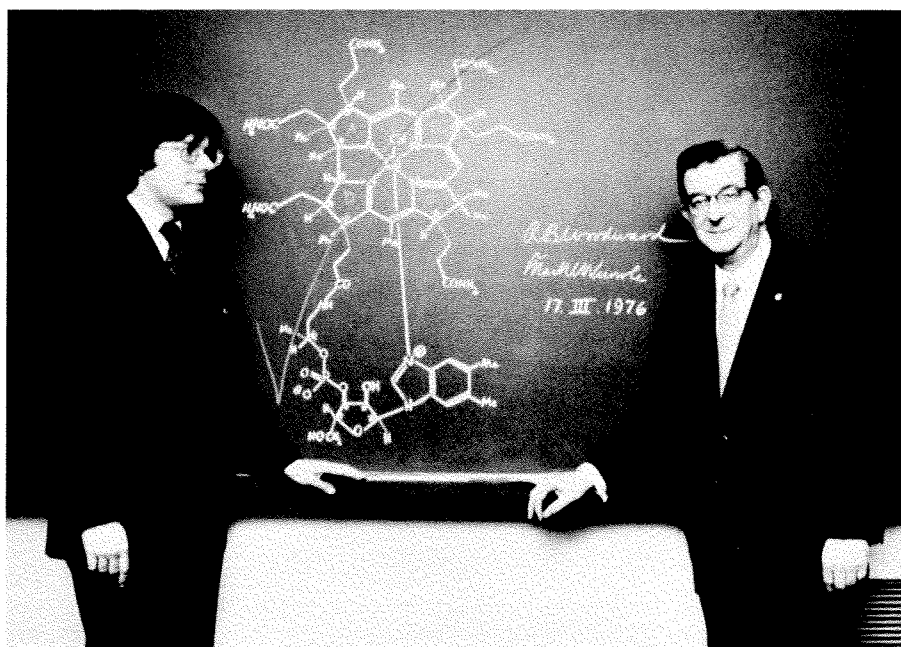


Fig. 7. Mark Wuonola and RBW announce the completed synthesis of vitamin B₁₂.

Footnotes:

- 1) F. Wöhler, *Ann. d Physik*, **12**, 253 (1828).
- 2) F. Wöhler and J.v. Liebig, *Justus Liebigs Ann. Chem.*, **26**, 254 (1838).
- 3) This article is written as an appreciation of all that Woodward has done for chemistry in general and for me in particular, and is dedicated to him on the anniversary of his sixtieth birthday. If at any stage the reader should feel that my personal account transgresses the bounds of gentlemanly behavior, then I would refer them to the first piece of advice that Woodward ever gave me: "David, there is not time enough to worry over what others think about you."
- 4) I thought of changing your name, Pat, but I know, and you know, and he knows where the story comes from, so what's the point?
- 5) R. Anschütz, "August Kekulé 1829-1896" in *Great Chemists*, ed. E. Farber, *Interscience*, New York, 1961, p. 697.
- 6) Sigmund Freud, *The Interpretation of*

Dreams, trans. A.A. Brill, completely revised edition (London: George Allen and Unwin, Ltd., 1937).

- 7) F. Haber, "Justus von Liebig 1803-1873" in *Great Chemists*, ed. E. Farber, *Interscience*, New York, 1961, p. 535.
- 8) In addition to papers, dedicated to Woodward on the occasion of his sixtieth birthday, which will be published throughout the scientific literature, *Heterocycles*, under the editorship of Tetsuji Kametani, will publish an issue containing papers dedicated to Woodward.
This year's Leermakers Symposium, to be held at Wesleyan University three weeks after Woodward's birthday, is to be built around the impact Woodward has made on total synthesis. Additional information on the symposium, of which Woodward is the Honorary Chairman, can be obtained from Professor Max Tishler, Department of Chemistry, Wesleyan University, Middletown, CT 06457.
- 9) David Dolphin.



David Dolphin

About the Author

After obtaining his Ph.D. with Alan Johnson in 1965 David Dolphin spent a year's postdoctoral fellowship with Woodward, and he then joined the faculty of the chemistry department at Harvard where he stayed for eight years, moving in 1974 to his present location at the University of British Columbia.

Handling Air-Sensitive Reagents

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A large variety of air-sensitive reagents is available from Aldrich. Specific examples include solutions of borane complexes, organoboranes, borohydrides, Grignard reagents, organoaluminums, organolithiums, and organozincs. Since all of these reagents react with water or oxygen or both, they must never be exposed to the atmosphere.

Most modern synthetic chemists are familiar with the utility of these versatile organometallic reagents. However, because the compounds are air-sensitive or pyrophoric, some workers hesitate to make use of the remarkable chemistry of these reagents. Some chemists still believe that very specialized equipment and complicated techniques are required for handling air-sensitive reagents. This is often not the case.

Air-sensitive materials can be separated into two categories: those which react catalytically with air and/or water and those which react stoichiometrically. In the latter case, which fortunately includes most of the synthetically useful reagents, the reagents can be handled easily on a laboratory scale using syringe and syringe-related techniques. The catalytically sensitive materials often require the use of more sophisticated apparatus such as vacuum lines, Schlenk-apparatus, or inert-atmosphere glove boxes.

Brown and coworkers have recently described simple, convenient bench-top methods for handling stoichiometrically sensitive compounds on a laboratory scale.¹ Shriver has presented an excellent description of the more sophisticated techniques used to manipulate catalytically sensitive materials.²

The present discussion is limited to those techniques necessary for handling air-sensitive reagents on a preparative scale. In addition, several pieces of specialized equipment which greatly facilitate the safe and effective handling of these reagents will be described. The book by Brown and coworkers should be consulted for more detailed descriptions of simple techniques for working with air-sensitive materials.

Air-sensitive reagents available from Aldrich are packaged in special bottles. The Aldrich Sure/Seal packaging system (Fig. 1) provides a convenient new method for storing and dispensing research quantities of air-sensitive reagents. With this

discussion at this point will illustrate the convenience of the new Sure/Seal packaging system.

The Bakelite cap on a Sure/Seal bottle can be safely removed because the crown cap, with its Teflon/elastomer liner, is already crimped in place. The reagent can then be dispensed using a syringe or double-tipped needle inserted through the hole in the metal crown cap. After the needle has been withdrawn from the bottle, a small hole will remain in the Teflon/elastomer liner. Under normal circumstances, the hole in the liner will self-seal and the reagent will not deteriorate. However, the possibility exists that once an elastomer liner is punctured, it may leak on long-term storage. This possibility is virtually eliminated with the Sure/Seal system because when the Bakelite cap is replaced, the Teflon/elastomer liner in the cap forms a seal against the top of the metal crown. Thus, the contents are effectively protected from moisture and oxygen in the atmosphere.

Reactions involving our air-sensitive reagents may be carried out in common ground-glass apparatus. The only additional equipment required is a source of inert gas, a septum inlet, a bubbler, and syringes fitted with suitable needles. Aldrich offers a variety of septums, syringes and syringe-related hardware, several pieces of septum-inlet-equipped glassware, and a bubbler.

Laboratory glassware contains a thin film of adsorbed moisture which can be easily removed by heating in an oven (125°/overnight or 140°/4 hrs). The hot glassware should be cooled in an inert atmosphere by assembling the glassware

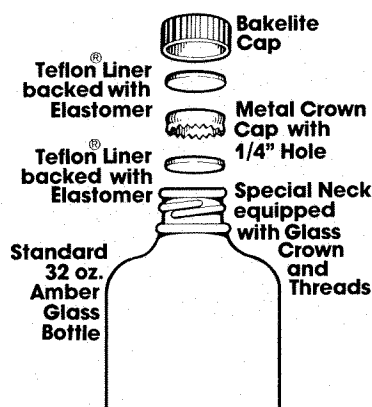


Fig. 1. The Aldrich Sure/Seal packaging system.

new bottle, reactive materials can be handled and stored without exposure to atmospheric moisture or oxygen. The reagent comes in contact only with glass and Teflon®, yet it can be readily transferred using standard syringe techniques.

Syringe transfer techniques will be described in more detail later, but a short

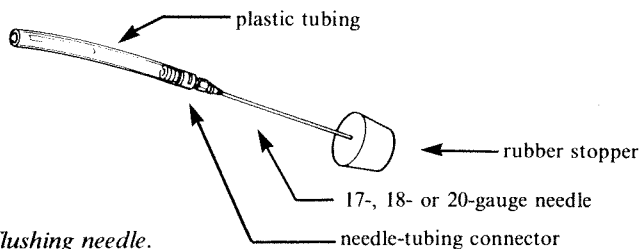


Fig. 2. Nitrogen-flushing needle.

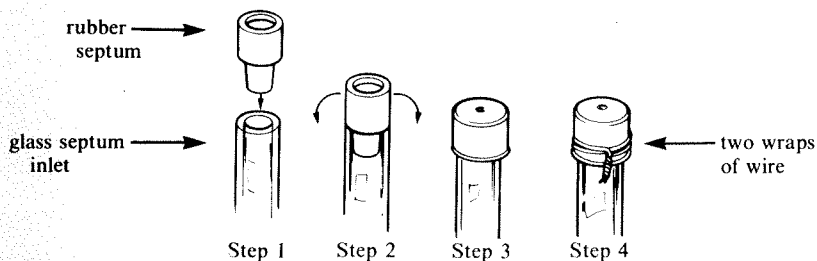


Fig. 3. Procedure for utilization of rubber septum.

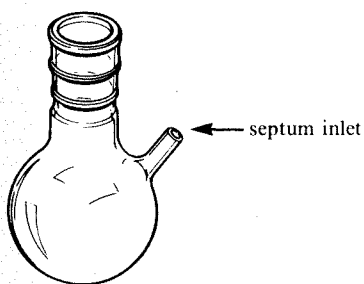


Fig. 4. Flask equipped with septum inlet.

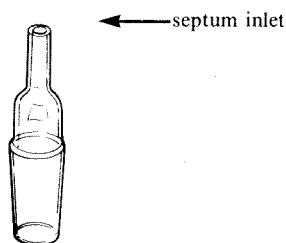


Fig. 5. Septum inlet adapter.

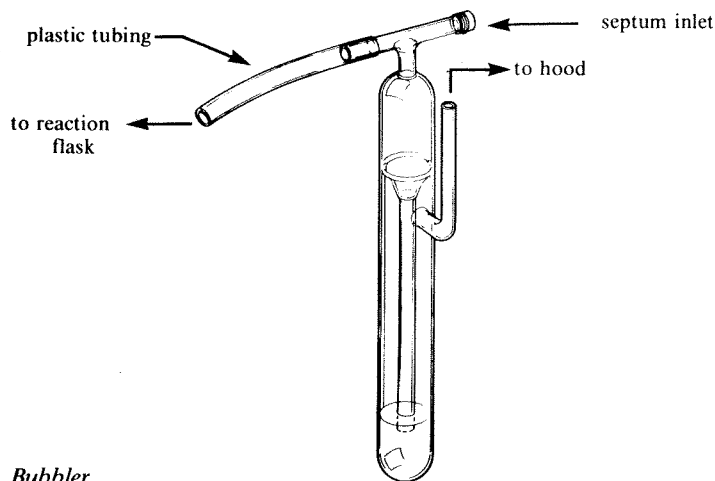


Fig. 6. Bubbler.

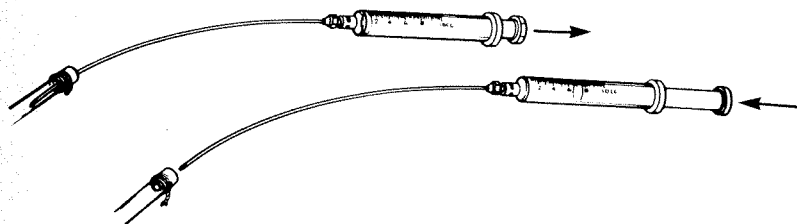


Fig. 7. Flushing a syringe with nitrogen.

while hot and flushing with a stream of dry nitrogen or argon. A thin film of silicone or hydrocarbon grease must be used on all standard taper joints to prevent seizure upon cooling. Alternatively, the apparatus may be assembled cold and then flamed with a Bunsen burner while flushing with dry nitrogen.

The oven drying procedure is more efficient than flaming with a burner because it removes moisture from inner surfaces of condensers and from other intricate parts. Spring clips or rubber bands are required to secure joints during the flushing since the nitrogen pressure may open the seals of unsecured standard taper joints, especially when the joints are hot.

Only high-purity, dry nitrogen from a cylinder with a pressure regulator (adjusted to 3-5 psi) should be used for flushing. Plastic tubing (Aldrich Catalog No. Z10,119-2) can be used to connect the nitrogen line to a tube connector adapter (equipped with a stopcock) on the reaction apparatus. Nitrogen may also be introduced through a rubber septum via a hypodermic needle connected to the end of the flexible tubing on the nitrogen line. The needle-tubing connector (Aldrich Catalog No. Z10,116-8) provides a simple method for attaching the needle to the tubing. When not in use, this nitrogen-flushing needle (Fig. 2) should be closed by inserting the needle into a solid rubber stopper to prevent diffusion of air into the needle when the nitrogen supply is turned off.

Large rubber septums may be used to cap female joints. However, the use of 6-mm septums and 8-mm o.d. standard wall or 9-mm o.d. medium wall (6-mm i.d.) glass septum inlets is preferred. The small rubber septum (Aldrich Catalog No. Z10,072-2) provides a more positive reseal after puncture and allows less rubber to be in contact with organic vapors in the reaction vessel. The use of 9-mm o.d. medium wall tubing, instead of the more common 8-mm o.d. standard wall, with 6-mm septums is preferred. With the medium wall tubing, the 6-mm septum not only fits the inside diameter of the glass tube but also fits snugly over the outside when the top is folded over (Fig. 3). The glass septum inlet can be built into the reaction flask (Fig. 4) or placed on an adapter (Fig. 5) for use with unmodified glassware.

The rubber septum may be wired in place as shown in Figure 3. However, if the 6-mm septum is properly fitted to 9-mm medium wall tubing, the wiring step may be omitted unless high pressures (>10 psi) are expected.

To maintain an air-tight system the reaction vessel must be vented through a mer-

cury or mineral oil bubbler. Obviously, simple drying tubes will *not* prevent oxygen from entering the system. At all times during the reaction, the system should be under a slight positive pressure of nitrogen as visually indicated by the bubbler. Figure 6 illustrates a suitable bubbler (Aldrich Catalog No. Z10,121-4).

A pressure reversal in the reaction vessel may cause the liquid in the bubbler to be sucked back. The enlarged head space in the bubbler will minimize the danger of the bubbler liquid being sucked back *into the reaction vessel*. However, if a large pressure reversal occurs, *air will be admitted* into the reaction vessel. The T-tube bubbler shown can be used to prevent this problem because nitrogen pressure can be introduced intermittently through the septum inlet. The problem can be completely eliminated by a slow and continuous nitrogen flow.

When the assembled (nitrogen-flushed) glassware has cooled, air-stable solids may be introduced through an entry port under a blanket of nitrogen. The entry port is closed and the system is flushed with nitrogen.

Small quantities (up to 50ml) of air-sensitive reagents and dry solvents may be transferred with a syringe equipped with a needle (length 1-2ft). The long needles are used to avoid having to tip reagent bottles and storage flasks. Tipping often causes the liquid to come in contact with the septum. Contact of rubber septums with many organic liquids causes swelling and deterioration of the septums, and should therefore be avoided.

A rubber septum in contact with organic vapors provides a positive seal for only a limited number of punctures, depending upon the needle size. The lifetime of the septum may be extended by always reinserting the needle through an existing hole. It is also advantageous to put a layer of silicone or hydrocarbon grease on a rubber septum to facilitate passage of the needle through the rubber and to minimize the size of the hole in the septum. Ideally, the syringe and needle should be dried in an oven prior to use. Naturally, the syringe body and plunger should *not* be assembled before being placed in the oven. The syringe should be flushed with nitrogen during the cooling. A syringe may also be flushed 10 or more times with dry nitrogen as illustrated in Figure 7 to remove the air and most of the water adsorbed on the glass. A dry syringe may be closed to the atmosphere by inserting the tip of the needle into a rubber stopper.

The syringe-needle assembly should be tested for leaks prior to use. The syringe is

half filled with nitrogen and the needle tip is inserted in a rubber stopper. It should be possible to compress the gas to half its original volume without any evidence of a leak. A *small* amount of stopcock grease or a drop of silicone oil placed on the Luer lock tip will help insure tightness.

The syringe transfer of liquid reagents is readily accomplished by first pressurizing the Sure/Seal reagent bottle with dry, high-purity nitrogen followed by filling the syringe as illustrated in Figure 8. The nitrogen pressure is used to slowly fill the syringe with the desired volume plus a slight excess (to compensate for gas

bubbles) of the reagent. Note that the nitrogen pressure pushes the plunger back as the reagent enters the syringe. The plunger should not be pulled back since this tends to cause leaks and creates gas bubbles. The excess reagent along with any gas bubbles is forced back into the reagent bottle as illustrated in Figure 9. The accurately measured volume of reagent in the syringe is quickly transferred to the reaction apparatus by puncturing a rubber septum on the reaction flask or addition funnel, as shown in Figure 10. Syringes with capacities up to 100ml are available. However, the large syringes become

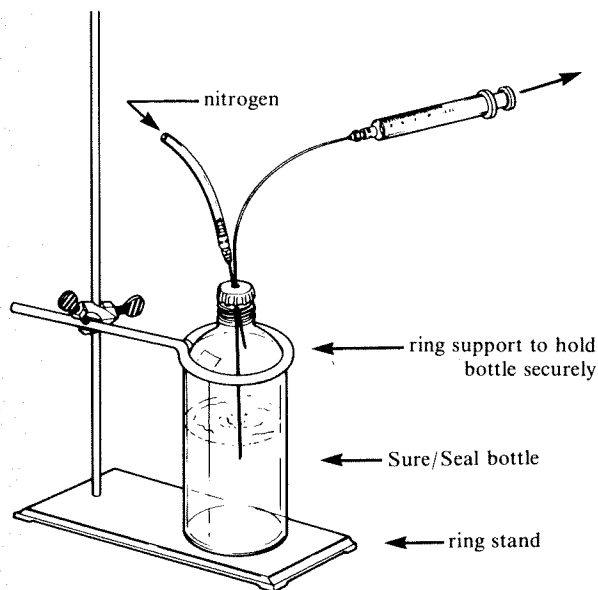


Fig. 8. Filling syringe using nitrogen pressure.

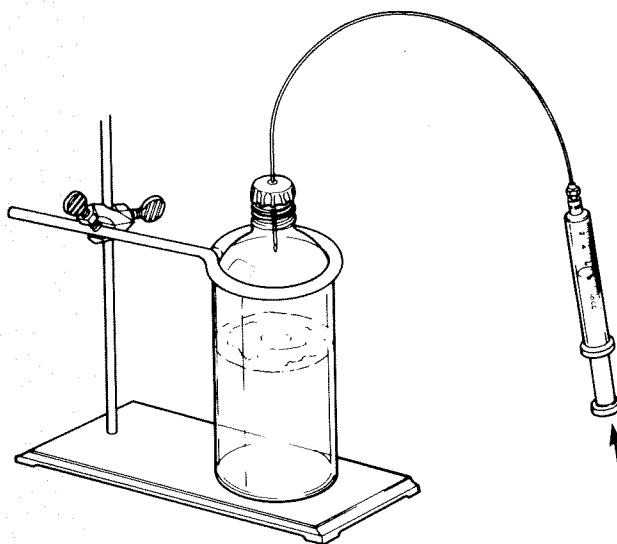


Fig. 9. Removing gas bubbles and returning excess reagent to the Sure/Seal bottle.

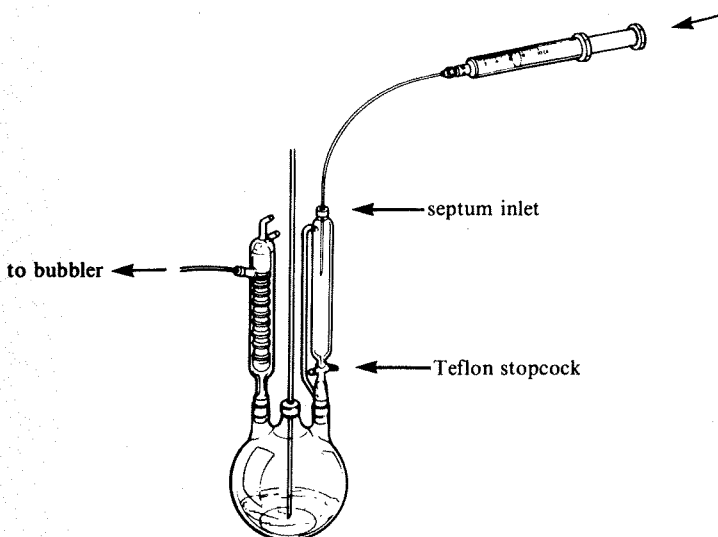
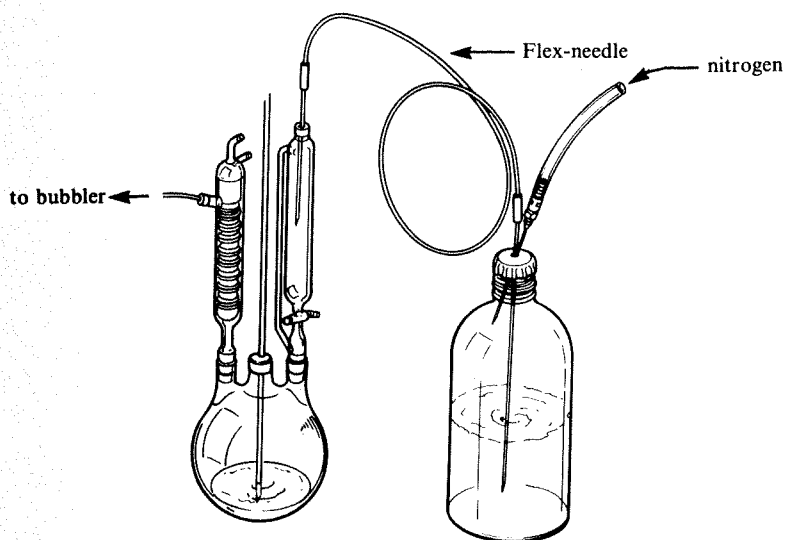


Fig. 10. Syringe transfer of reagent to reaction vessel.



awkward to handle when completely full.

When the transfer of more than 50ml of solvent or liquid reagent is required, it is generally much more convenient to use the double-tipped needle technique. Figure 11 illustrates liquid-reagent transfer under nitrogen pressure using this technique.

To accomplish the double-tipped needle transfer, the needle is first flushed with nitrogen. The Sure/Seal bottle is pressurized with nitrogen using the nitrogen flushing needle. The double-tipped needle is then inserted through the septum on the reagent bottle into the head space above the reagent. Nitrogen immediately passes through the needle. Finally, the other end of the double-tipped needle is inserted through the septum on the reaction apparatus, and the end of the needle in the

reagent bottle is pushed down into the liquid. The volume of liquid reagent transferred is measured by using a calibrated flask or addition funnel. When the desired volume has been transferred, the needle is immediately withdrawn to the head space above the liquid, flushed slightly with nitrogen, and removed. The needle is first removed from the reaction apparatus and then from the reagent bottle.

An alternative method for transferring measured amounts of reagents is shown in Figure 12. The reagent is first transferred via a double-ended needle from the Sure/Seal bottle to a dry, nitrogen-flushed graduated cylinder equipped with a female F joint and a double inlet adapter (glassware G as illustrated in equipment section). Only the desired amount of

reagent is transferred to the cylinder. The needle is then removed from the Sure/Seal bottle and inserted through the septum on the reaction apparatus. By applying nitrogen pressure as before, the reagent is added to the reaction apparatus. If it is necessary to add the reagent slowly, a modified double-tipped needle can be used. This useful transfer needle is constructed from two long standard needles and a male Luer lock to male Luer lock syringe valve (accessory O as illustrated in equipment section). The valve may be opened slightly allowing only a very slow flow of reagent. Thus, the addition funnel is not needed and many reactions can be carried out in single-necked flasks as shown in Figure 13.

The 12-gauge stainless steel needles on the Flex-needle provide a rapid means of transferring air-sensitive reagents under nitrogen pressure. However, the needles are so large that once the crown cap liner on the Sure/Seal bottle is punctured, the liner will not self-seal. If only a portion of the contents is to be used up, a needle no larger than 16-gauge should be utilized. By using small needles and by always tightly replacing the Bakelite cap, the reagent in a Sure/Seal bottle will not deteriorate even after numerous septum punctures. However, if the reagent is to be used repeatedly for small-scale reactions or if an unused portion is to be stored for an extended length of time, the material should be transferred from the Sure/Seal bottle to a suitable storage bottle. One type of container (Aldrich Catalog No. Z10,248-2) for air-sensitive reagents is shown in Figure 14. Alternatively, an appropriate adapter (Fig. 15) can be used to convert a round-bottomed flask into a storage vessel.

The Teflon stopcock on the storage bottle keeps solvent vapors away from the septum, thereby minimizing swelling and deterioration of the septum. Furthermore, the stopcock allows for replacement of the septums. A change of septums is sometimes necessary because they tend to deteriorate on prolonged standing in a laboratory atmosphere.

Naturally, this storage bottle must be oven-dried and flushed with nitrogen before use. A clean and dry Flex-needle should be used to transfer the contents of the Sure/Seal bottle to the storage bottle, using the standard double-tipped needle technique.

Clean-up of equipment that has been used to transfer air-sensitive reagents must not be taken lightly. Since many of these reagents react violently with water, fires are a potential hazard. The crown cap and liner of an "empty" Sure/Seal bottle should be removed and the open bottle placed in a hood to allow the last traces of reactive

reagent to slowly air-hydrolyze and oxidize. After at least a day, the inorganic residue can be rinsed out with water. Empty storage bottles and storage flasks should be treated similarly. Air-hydrolysis in a hood is appropriate only for the last traces of material that remain after a Sure/Seal bottle has been emptied as completely as possible *via* syringe or double-ended needle transfer. The Aldrich Catalog/Handbook should be consulted for the recommended disposal procedures for larger amounts of reactive chemicals.

All syringes and needles that have been used to transfer air-sensitive materials must be cleaned *immediately* following use. Also, in general, a syringe should only be used for a single transfer. Failure to follow this practice will invariably result in plugged needles and "frozen" syringes due to hydrolysis or oxidation of the reagents. The double-tipped needles are flushed free of reagent with nitrogen in the transfer system, and then immediately removed and placed in a clean sink. With water running in the sink and in the complete absence of flammable solvents and vapors, the double-tipped needles or Flex-needle can be rinsed with water. When activity in the rinse water is no longer observed, acetone from a squeeze bottle can be flushed through the needle. Depending on the reagent transferred, it may be necessary to use dilute aqueous acid or base from a squeeze bottle to remove inorganic residue that is not water-soluble.

Following its use, a syringe contains a larger residual amount of reagent. It is advisable to rinse out the reactive reagent by first placing a few milliliters of the *same* solvent that was used for the reagent in a small Erlenmeyer flask in the hood. Keeping the needle tip under the solvent at all times, no more than half the solvent is then sucked into the syringe until the syringe is at least half-full. The solvent plus dissolved residual reagent is ejected from the syringe back into the same Erlenmeyer flask. This rinsing treatment is repeated at least three times. The wash solution can be safely combined with other waste solvents for eventual burning, and the syringe may be further cleaned with water and acetone in the sink. Again, treatment with dilute aqueous acid or base may be necessary.

Once the syringe needles and double-tipped needles have been rinsed in a sink, they can be further cleaned and dried using a device similar to that shown in Figure 16. Needles are cleaned by inserting them through the septum. Vacuum from a water aspirator is used to pull solvents from squeeze bottles through the needles. After pulling air through the system for a few minutes, the syringe plus needle or the

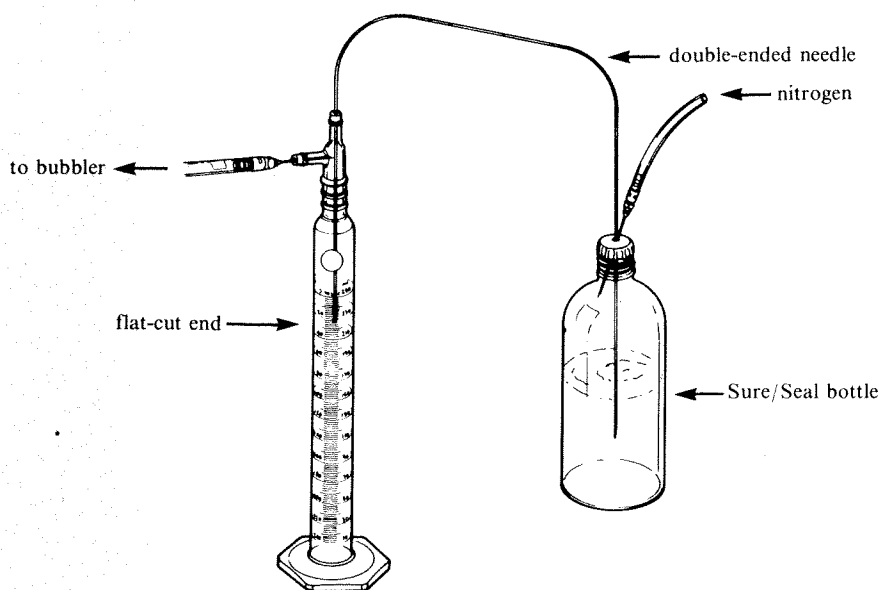


Fig. 12. Double-ended needle transfer to graduated cylinder.

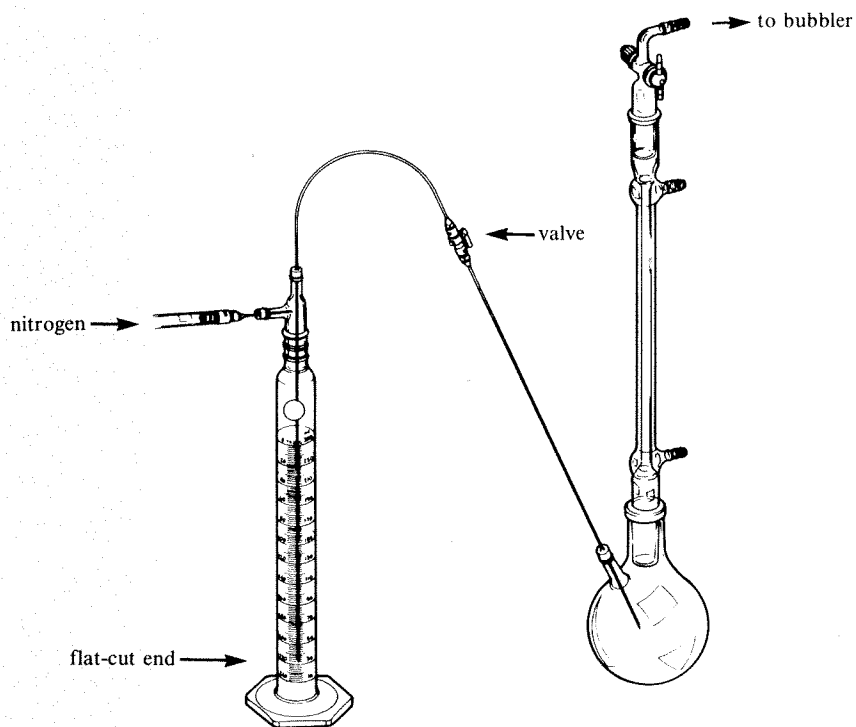


Fig. 13. Double-ended needle transfer with syringe valve.

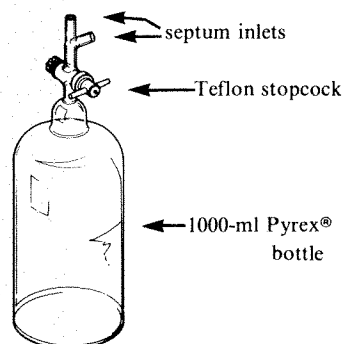


Fig. 14. Storage bottle equipped with Teflon stopcock.

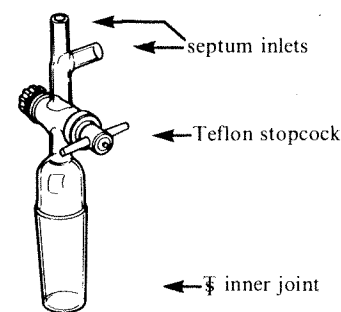


Fig. 15. Septum inlet adapter for storage flask.

double-tipped needle will be dry. The syringe plunger should be replaced in the barrel for storage. If a syringe plunger and barrel are not assembled for storage, dust can settle on the plunger and in the barrel. Upon reassembly, these fine particles will occasionally scratch the barrel or cause seizure of the plunger in the barrel. However, the plunger and barrel must be disassembled before oven drying.

Most of the above techniques were developed for handling various organo-borane reagents. However, these methods are applicable to other air-sensitive materials.

When handling air-sensitive materials, it is important that the user be thoroughly familiar with the basic chemistry of the reagent. Also, the user should be prepared for unexpected problems. For example, at least one extra set of clean, dry syringes and needles or double-tipped needles should always be available in case the first set of equipment becomes plugged.

As in all laboratory practices, simple "common sense" is required. It is impossible to describe in detail the techniques required for all possible situations. As a rule-of-thumb, the chemist working with these air-sensitive reagents should always keep in mind that, if at all possible, these solutions

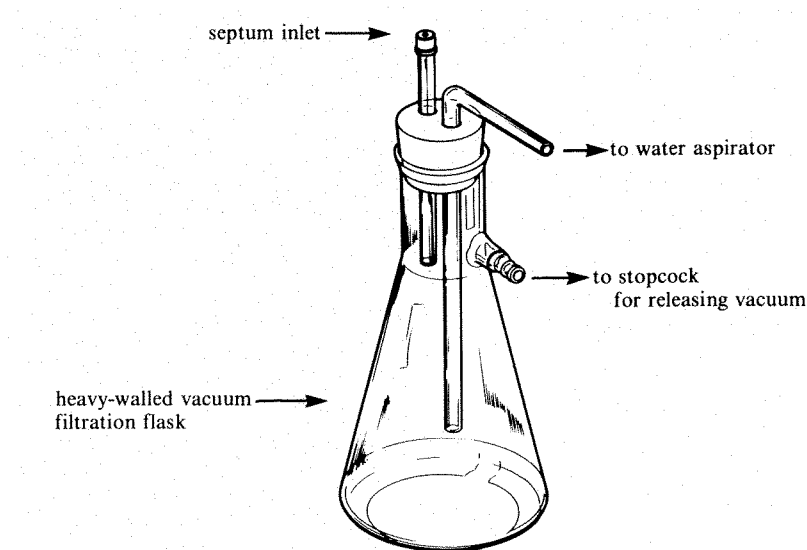


Fig. 16. Needle cleaning and drying apparatus.

should never be allowed to come in contact with the atmosphere.

Finally, it is our sincere hope that with the convenience of our new Sure/Seal packaging system, coupled with simple, convenient syringe techniques, no technically qualified chemist will ever again hesitate to use air-sensitive reagents.

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1) G.W. Kramer, A.B. Levy, and M.M.

Midland in H.C. Brown, "Organic Syntheses via Boranes," John Wiley and Sons, Inc., New York, N.Y., 1975 (Aldrich Catalog No. Z10,144-3, \$17.50).

2) D.F. Shriver, "The Manipulation of Air-sensitive Compounds," McGraw-Hill Book Company, New York, N.Y., 1969.