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VOLUME 1, NUMBER 1, 1968

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ABOUT THE COVER

The classical alchemical painting reproduced on the front cover was done by Thomas Wyck, a Dutchman of the second half of the 17th century. This painting and other works of art are described on page 6.

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Aldrichimica Acta replaces the previously published *Kardindex Sheets* to keep chemists informed of the latest chemical offerings by Aldrich Chemical Company, Inc. The articles also published are of general interest to users of chemicals and Aldrich customers. While the information and data included in this publication is correct and reliable to the best of our knowledge, it is not guaranteed to be so. Therefore, we cannot assume responsibility connected with the use of our chemicals or data. The information on or sale of any material is not intended as a license to operate under, or a recommendation to infringe, any patent covering any material or use.

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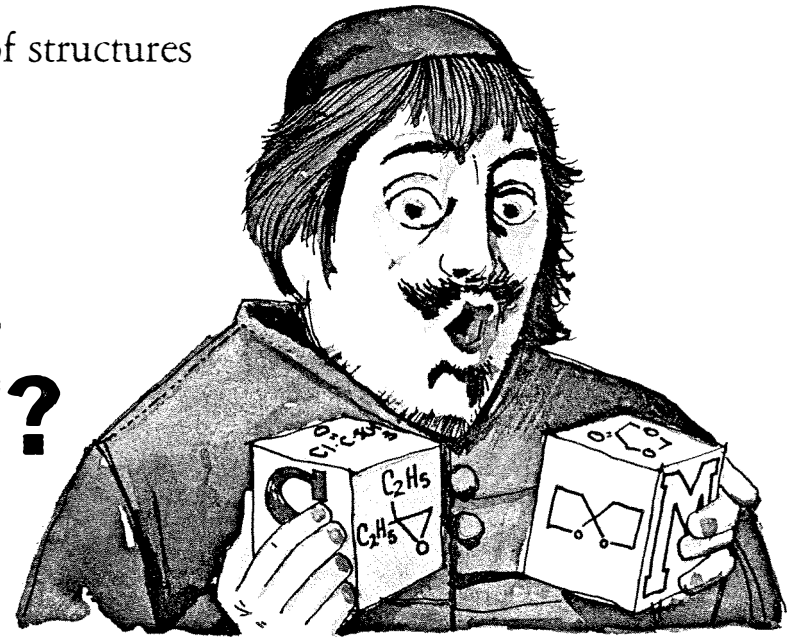
Fragment information retrieval of structures

William F. Buth: Aldrich Chemical Company, Inc.

wouldn't he be surprised?



If our bearded friend happened to be a chemist, vintage 1600 or so, wouldn't he be dumbfounded by the number and variety of organic chemicals available through the Alfred Bader Rare Chemical Division?

However, today's chemists plagued with an ever increasing mountain of journals, advertisements, data sheets, free trade publications, etc., have reason to feel frustrated with just the tremendous amount of information that would have gratified our old friend.

The advent of the computer of course has been a bright promise of help for the near future. Perhaps your company has a computer now! Perhaps it has had one for some time. It may be quite a while, however, before you will personally derive any benefits from your in-house information retrieval system. In most companies billing and sales analysis take precedence over other applications at the onset. Over 2½ million organic chemicals have been synthesized but to most chemists today, except for the promise of great things coming, the only way to find the literature or chemicals needed would be the same as our ancient friend's.

HELP IS AT HAND FOR YOU! ! Until your own computer department can find the time for you, Aldrich will make available to you *at no cost* the facilities of our own computer.

We can't help with your literature searching, but if the chemical you need or something similar to it is (or has been) available from the Aldrich or ABC Rare Chemical listings, our computer will find it for you.

It can find whole families of compounds or just the one you would like to have, if we have it in our present combined listing of 15,000 organic chemicals.

The ALDRICH FIRST° System

Although a number of systems for coding structures are available, they have either been oriented toward punched-card sorting equipment[1] which is a severe limitation in terms of time and flexibility or are too complex to allow rapid and economically practical coding and retrieval[2, 3].

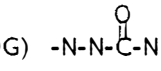
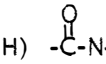
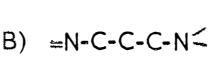
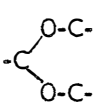
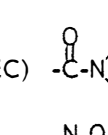
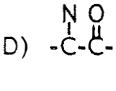
° Fragment Information Retrieval of Structures

The ALDRICH FIRST° system has been designed to use the great speed and flexibility of a modern computer[4] and, above all, to be simple.

Basically, the ALDRICH FIRST system uses a structural fragment approach in which the geometry of the chemical is charted, not its chemical characteristics. For example, phenol is a compound containing a hydroxyl group (C-O-H) and a six-membered carbon ring. The fact that it forms sodium salts is not considered because there are hindered phenols that do not form salts, but this is chemical information that might not be available to the person doing the preliminary coding of the chemicals. Therefore, degree of reactivity or any other characteristic of a chemical related primarily to its chemistry and not to its configuration is ignored.

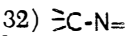
A large number of fragments were assigned code numbers. The ALDRICH FIRST° program can ask for combinations of fragments and in addition, exclude coded fragments.

Five Atom Groups

C Only	C and O	C, O and N
DA) 	DD) 	DG) 
DB) 	DE) 	DH) 
DC) 	DF) 	EB) 
	DY) 	EC) 
	EG) 	ED) 

For example

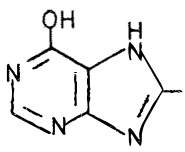
1.) A request for code groups 79)

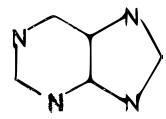
and 32) 

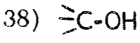
would retrieve all amino acids.

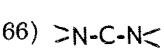
2.) If the same request excluded code group 37) C-SH then all amino acids except those containing mercaptan groups would be retrieved.

The structural fragments selected for coding conform more to combinations of 2, 3 or 4 atoms from a geometrical point of view than to actual chemical functional groups. Overlap in coded groups is allowed and considered desirable.

 would be coded

MS) 

38) 

66) 

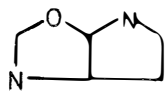
Over 250 fragments are used in this type of coding. Additional fragments are added from time to time but since position is not coded, further additions will be few.

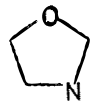
Ring Notation

Provision has been made for coding and retrieving ring systems. Unsaturation is ignored. Free standing single rings are coded separately from fused ring systems. A number from three to twenty-nine indicates the number of atoms in each ring—larger rings are placed to the right. Just ahead of each ring number are placed any hetero atoms, in alphabetic order, increasing hetero complexity to the right.

For example

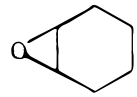
 = O5

 = N5NO5

 = NO5

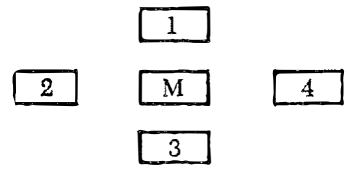
 = 6606

This system enables single rings to be retrieved even if they are part of a larger fused ring system. For example, 03 would retrieve all epoxy rings even if they occurred in the following ring system.

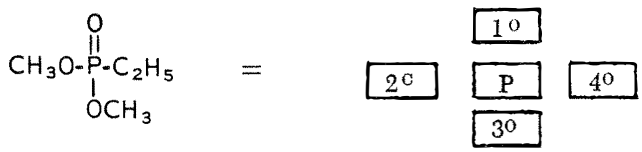
 =036

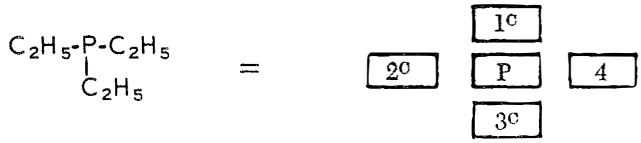
Metal-organic compounds

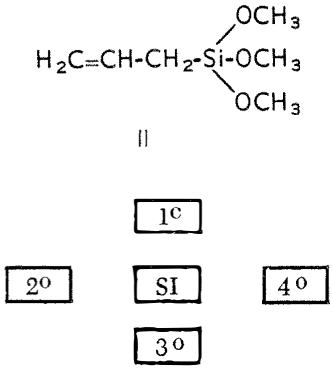
Certain phosphorus, sulfur, silicon and other atoms quite often constitute a "center of interest" and as such are independently coded in a geometric system. The element of interest is placed in the box denoted as M and surrounding elements are listed in alphabetic order around it in boxes 1-4. The number 1 box is reserved for multiply bonded atoms.



Chemists are inundated with literature.







Empirical Formula

Although it would be pointless to search for an exact empirical formula, since this could be looked up rapidly in a table, it is sometimes desirable either to search for or exclude certain elements. This has been programmed into the system together with the ability to retrieve an exact number of any element or elements such as compounds containing three oxygen atoms or two sulfur atoms, etc.

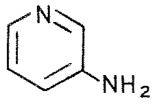
Performance and Retrieval Efficiency

The ALDRICH FIRST system was designed to retrieve pertinent information from an almost random selection of organic chemicals. It was hoped to hold noise levels (undesired retrievals) to fifty per cent or less. In practice this has varied widely.

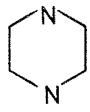
The retrieved grouping of chemicals always contains ALL of the desired chemicals exhibiting the requested information. The problem, of course, is that quite often, unexpected chemicals of *like* but not *obviously similar* characteristics are also retrieved.

Requests for CB) =N-C-C-N=

(diamines) will also retrieve



and

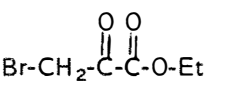


derivatives

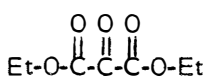
unless rings are restricted. However, second thoughts on either of these two groupings will indicate possible new areas of interest since they do really conform to a general diamine constraint.

Requests for CF)  (α-diketones)

will also retrieve chemicals such as



and



unless groups such as  and 

are excluded.

In many instances, it is just these "questionable" chemicals that represent the greatest value of an information retrieval system and primarily for this reason an excessively restrictive system has been avoided.

The old fashioned way: hunting through a forest of bottles.

What's in it for Aldrich?

The more pertinent chemicals that a customer sees, the higher the probability that he will buy some of those chemicals. Therefore we consider this service primarily a marketing tool. On the other hand, computer information retrieval of this scope is seldom available to the individual who could most benefit from it. We feel that we can offer the chemist a big plus factor in pursuing his daily work. In a previous article it was also pointed out that catalogs, which represent the biggest expense in any marketing operation, rapidly become obsolete. Placing new chemicals at the fingertips of interested chemists as soon as they become available is of *value*, both to Aldrich and its customers. The ALDRICH FIRST master file is kept current and lists of chemicals retrieved therefrom are as up to date as yesterday.

Please feel free to test us. Your requests will be handled promptly and treated confidentially.

REFERENCES

1. "Indexing Spectral Absorption Data," *American Society For Testing and Materials*, 1964.
2. Feldman, A., Holland, D. B., and Jacobus, D. P., "The Automatic Encoding of Chemical Structures," *J. Chem. Doc.*, *3*, *187* (1963).
3. Gluck, D. J., "A Chemical Structure Storage and Search System Developed at Du Pont," *J. Chem. Doc.*, *5*, *43* (1965).
4. National Cash Register (NCR) 315, CRAM system (Card Random Access Memory).

Chemistry and art

Alfred Bader: Aldrich Chemical Company, Inc.

When I was studying Chemical Engineering in Canada, most engineering students and many of the professors believed that science and art were immiscible—only sissies (a term applied to most Arts students) concerned themselves with the fine arts. Twenty years of chemistry and collecting old paintings have convinced me that we were wrong—the Sciences and Art are not only miscible, but can greatly help each other.

Personally I get as much pleasure from the synthesis of a new product or the elucidation of a structure as I do from finding that a painting bought in some junk store or in an obscure auction turns out on cleaning to be a thing of beauty by a known master.

Naturally chemistry and physics help in the restoration, in the determination of period and country, of how much is original and what later additions.

But art also can and does help chemistry. All of us know how Fisher Scientific's reproductions of alchemical paintings add beauty to many laboratories. These paintings, mainly 17th century Dutch and Flemish works of alchemists at work, were collected between the World Wars, when it was still possible to bring together such a fine collection—today an almost impossible task. The one alchemical painting I own (front cover), by Thomas Wyck, a Dutchman of the second half of the 17th century, is a real action painting. A master alchemist surrounded by the paraphernalia of his craft—including a skeleton blowing a trumpet—guides his lab technician in the magic circle—two candles, a cross, a skull, a bible, blood, the magic staff—to say the proper incantations to turn the base metal suspended from the ceiling into gold. It would make a fine advertisement for our work of art: "Today one book suffices: the Aldrich catalog." Such paintings with alchemical and medical subjects of course often challenge you to compose ads. For instance, take the painting (Fig. 1) of the doctor examining the urine of the girl. Clearly he has told her that she is pregnant and, with no wedding ring, she is in tears. What an ad this would make for a pharmaceutical company: "If only she had known the pill!"

When we first thought about putting a painting on the cover of our catalog, both our Director of Research and I were pretty much against the idea—would not an old master painting seem out of place on a scientific catalog? But our Director of Marketing won out: If we could pioneer the usable catalog—the first catalog with structures, classes of compounds and empirical formulae, we could also be the first to add beauty to our cover. We offered a reproduction of the cover, thinking that perhaps forty or fifty chemists would request it, and thus far over two thousand have—often with hilarious comments. To quote just one, from Stanford University:

> "The Art Appreciation Group of Dr. Djerassi's lab would like to have a copy of your Squill-Pitter, Pull-Squitter, Kill-Qutter, Cull-Squirter . . . the chap who hasn't heard about ball-points on your new catalog cover."

By the time we were ready for the Library of Rare Chemicals Catalog, it was just a question of which painting to use, and surely none could express surprise at such a catalog better than our Man Surprised. The only unexpected question I have had to answer several times by telephone from chemists who do not know me: "Is that perchance a painting of me?" If only I had that much hair!

Paintings on stamps have recently become most fashionable, but Aldrich is the only company I know that uses a painting on its stock-certificate, an early Rembrandt of a man studying, a painting also used on some of our advertisements (Fig. 2). Think how appropriate some paintings

Figure 1.

Figure 2.

might be on some stock certificates: Western Union of course would use a painting by Morse who not only invented the telegraph but was also one of our ablest American painters. Helena Rubenstein could show the Mona Lisa, or perhaps one of the many Dutch portrayals of a girl dressing; and perhaps we should suggest to one of our Milwaukee beer companies that they use the Delft brewer shown in Fig. 3 . I understand that the New York Stock Exchange has some pretty strict rules about the certificates of listed companies—but that is a bridge we can cross when we come to it, and we have a long way to go.

Last year Aldrich sent our collection of Dutch and Flemish 17th century paintings to Midland and this year to the Kalamazoo Art Institute—partly in the hope of course that many of our good customers at Dow and Upjohn would become even better customers—and at least a good many chemists visited the shows (Fig. 4). Perhaps the fact that a good many descendants of the Dutch artists represented in the show live in Michigan also helped.

Figure 3.

Few realize how many chemists are also amateur artists—even though the ACS Convention shows compare favorably with most regional exhibitions. Take William Buth, our Director of Operations, for instance. Bill is not only responsible for that fine back-cover on our library catalog, but recently won first prize in the Art Exhibit by Chemists at the Chicago ACS Convention for his wood sculpture (Fig. 5).

Clearly art and chemistry are miscible in all proportions.

Today *Tomorrow*

Figure 5.

Figure 4. From l. to r. Drs. Fred Bassett, Robert Levin and Douglas Shepherd of the Upjohn Company at the Kalamazoo Art Center Show of the Aldrich collection.

Reprinted by permission — *Modern Chemicals*

Youth on the way up

A portrait of Aldrich Chemical Company

Dr. W. Edward Higbee, Editorial Director, *Modern Chemicals*

In that vanished time before the War, a research man who needed intermediate compounds for his work—and you always did—usually made them himself. If he needed a fractionating column he was apt to build it himself. It was rather fun; you learned glassblowing and pipe fitting and some interesting insights on synthetic methods. But it took time, much time, away from your original objective.

Today it's different. Research directors have substantial budgets; even vice presidents understand that laboratory time spent in making intermediates is time wasted in pursuit of a potential profit—and thus money wasted. The problem becomes acute for organic, biochemical, pharmaceutical research groups who often must test whole series of related chemicals to prove or void a line of thought.

So, today a research man, needing a particular chemical or group of chemicals, usually buys from a company specializing in research chemicals. If he can't get the precise structure he wants a derivative or homologue is usually available which will do as well or act as intermediate.

This is Aldrich's business and they have been very successful in it over the last fifteen years. Aldrich Chemical supplies a full line of organic chemicals—common and rare, well or little known—to research and development men all over the world. For the most part these are for laboratory use although moderate quantities are sometimes shipped for pilot plant runs. Some products are even shipped in ton lots. Although nearly 9000 different organics are listed in Aldrich's latest catalogue, shipment of orders is prompt from their enormous inventory, now 97% complete in stock.

Aldrich's new catalogue is a fascinating thing to look into. There is a considerable section on analytical reagents, arranged both by formula and end use; indicators for pH, chelometry, adsorbtion, redox potential, fluorescence; dyes, tetrazolium salts and the like. Here too are more sophisticated reagents, 5,5′ *dithiobis (2-nitrobenzoic acid)* is effective in quantative determination of -SH groups. Certain trimethylsilyl derivatives of nonvolatile carbohydrates and polyols grow wings and can be estimated in the gas chromatograph. These can be made from Aldrich's *bis-(trimethylsilyl)-acetamide* or *hexamethyldisilazane*. There are many more.

Then there are fat sections listing what Aldrich calls "active intermediates", chemicals with active functional groups, with which something can be or has been *done*. Some, like those following, have already had press notices.

Adamantane, a chemical "bird-cage" built of four fused cyclohexane rings, is a many faceted medicinal building block. *Adamantanamine hydrochloride* is a potent antiviral agent.

N-methyl-N'-nitroso-N-nitrosoguanidine (MNNG or the "Magic Bullet") is a cancer research tool and mutagen.

N-methyl-N-nitroso-p-toluenesulfonamide is probably the most useful reagent for preparation of diazomethane.

3-hydroxypyridine is a widely used starting material for drugs.

Dicyclohexylcarbodiimide is useful in the synthesis of high molecular weight peptides.

Naturally, Aldrich has a high regard for quality control. The usual melting points and refractive indices are obtained routinely; typical values are included in the catalog while batch values are printed on container labels. However, these data are not considered sufficiently indicative of purity to be used alone for quality control purposes.

Instead, purity of initial preparations of every chemical listed is assured by a combination of methods which may include infra red assay for functional groups, ultra violet spectra, vapor phase and thin layer chromatography. A standard infra red spectrum is then taken with a Beckmann IR-5A or IR-8 and the spectrum of each subsequent batch is compared with this.

Aldrich does not make all these chemicals, or course. Imagine the laboratory space, the forest of equipment, the buzzing of PhD's necessary to produce and maintain stock in 9000 pure chemicals! They buy most (85% currently) from established chemical producers, both national and international in origin. This procedure gives a sound supply position to their products and also provides an invaluable marketing service to the individual manufacturers.

Chemical industry is a continual and inveterate spawner of new products. Large laboratory groups, e.g., those at Dupont, Allied, BASF, uncover and often patent new organics at the rate of many a day. These are fascinating things to the research men, yet . . . for the most part . . . they have no obvious end uses. Still, some must find commercial application to justify their costs of origin.

Another way in which a new chemical becomes available may occur when this is an intermediate in a particular chemical process. When excess capacity for this intermediate exists, it becomes imperative to try to find additional outlets for this capacity. A good example is *diphenolic acid*, a floor wax intermediate. The manufacturer who uses this compound in his process makes quantities available in the hope of finding additional volume outlets. Another example is *sodium hydride*, an intermediate in production of sodium borohydride. Again, there is more capacity for NaH than needed and additional outlets—perhaps as a superior coupling agent—are being sought. Aldrich saw

an opportunity here and founded Alfa Inorganics, in joint venture with Ventron Corporation. Located in Beverly, Mass., Alfa stocks and offers a wide variety of research *inorganics.*

Sometimes a product has only one large end use and its producer would like to find other applications. *Butyllithium* is a case in point. There are two major producers of butyllithium in this country, each of whom has one large customer using tonnage quantities as a stereospecific polymerization catalyst. Both companies would like to find additional outlets for their excess capacity and so are promoting butyllithium in research quantities.

Development of markets for new chemicals for which no end uses are known is one of the more frustrating tasks of the marketing people. Direct promotion through market surveys and sales calls, advertisements and sampling is expensive and can be wasteful when you don't even know if a market exists let alone where it lies.

An alternate method is market development through a distributor/reseller. The manufacturer produces a batch of his new chemical and sells it to the distributor. The distributor repackages this material and offers it through his catalog to chemists in R & D and screening programs throughout this country and often throughout the world. Aldrich, for example, adds about 150 new listings every three months. Inquiries for commercial quantities of such new chemicals are referred to the original producer.

Reputable distributors like Aldrich, for organics, or Alfa, for inorganics, can offer a much wider market exposure to any new chemical than its manufacturer could ever get alone. In addition to exposure in research laboratories, there are a large number of screening programs in this country which regularly purchase all new offerings of various distributors for inclusion in their work. These include the screening programs of the NIH and various other governmental laboratories and hospitals and those of several industrial organizations. Such programs can uncover uses and applications which would otherwise not be dreamed of, yet it is very difficult for someone who does not regularly serve these screening programs to learn where they are and how one gets inside. Also, as a result of these screening programs, a distributor is willing to accept for trial distribution and resale via his catalog almost any new chemical offered to him. He knows that a sufficient number of these programs will buy a small quantity of the new product from him adequately to cover his costs.

Aldrich Chemical Company was not the first nor is it the largest in its field. At least two other highly respected firms are older and wealthier. But Aldrich has shown remarkably good, steady growth in the sixteen years since its birth; in sales, in variety of products offered, in customer repute. Founded in 1951 in a Milwaukee garage, Aldrich sold $1,700 worth of chemicals that year. In ten years annual sales were over $1,000,000; in 1966 they reached $2,302,133.

Well, Aldrich is still young. Some of you may remember another chemical company also born in a garage, but in Detroit back in 1928. Today it's called Reichhold Chemicals with 1966 gross sales of $136,712,000.

Profits have not kept pace with sales mainly because expansion has been financed entirely from income. However, planned increases in size, capacity and personnel of various departments; installation of computer systems; expansion of sales and advertising programs are said to be pretty well completed. With decreased overhead, future sales growth may well be accompanied by a brighter profit picture.

Aldrich's staff is notable for technical ability, dedication, efficiency . . . and charm.

Available literature

1-Pyrrolidinecarbodithioic acid, ammonium salt (APDC) is widely employed for the determination of trace quantities of metals by atomic absorption spectrophotometry in a wide variety of materials ranging from agricultural matter such as fertilizers, plants and soils to clinical specimens such as urine, semi-conductors and related materials in the electronics industry and pollutants in water.
Product No. 14,269-7

Cyanomethylating Agents. Cyanomethyl benzenesulfonate and cyanomethyl p-toluenesulfonate are excellent cyanomethylating agents for primary, secondary and tertiary amines.
Product No. 14,460-6

trans. -1, 2-Cyclobutanedicarboxylic acid and a number of its derivatives have recently become available as new basic building blocks.
Product No. 14,531-9

1, 5-Diazabicyclo[5.4.0]undec-5-ene (DBU) and *1, 5-Diazabicyclo[4.3.0]non-5-ene* (DBN), the most versatile dehydrohalogenating agents known. Both are much more reactive than the amines traditionally used, and therefore much milder conditions can be employed.
Product No. 13,900-9

Diazoalkanes, seven precursors for the preparation of diazoalkanes (more will soon be added). Methods of preparation and literature references are available.

N,N-Dichlorourethan (DCU), a new reactive pseudohalogen, is now available in commercial quantities at substantially reduced prices.
Product No. 14,209-3

Liquid Crystals. Ask for our list of liquid crystals available from stock.

DL-α-Methyltyrosine is a specific blocking agent in the endogenous biosynthesis of catecholamines.
Product No. 12,069-3

Pyrrole, high purity (99%), is now available in commercial quantities at substantially reduced prices. Extensive literature review.
Product No. 13,170-9

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Aldrichimica acta

Volume 1, Number 2, 1968

PUBLISHED BY THE ALDRICH CHEMICAL COMPANY, INC.

ABOUT THE COVER

Our chemist who collects Dutch paintings recently acquired this hitherto unpublished large (180 x 207 cms.) painting of Tobias healing his blind father, by the Dutch Rembrandt student, Paulus Lesire. The story of Tobias and Tobit was a favorite subject of baroque painters, and it is particularly charmingly depicted here with the most life-like angel Raphael, Tobias' mother, Hannah, and even Tobias' faithful companion, his dog (the only friendly dog in the Bible) getting into the act.

Lesire is known mainly for his portraits, and this is his only known biblical painting; luckily, it is fully signed. But beside the art-historical interest in this painting, we were charmed by its obvious human interest: the love and concentration of the son healing his father—a model for every doctor everywhere.

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ALDRICHIMICA ACTA

Volume 1, Number 2
1968

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Milwaukee, Wisconsin

Editor, Richard K. Vitek

Assistant Editor, Kathleen D. Ryan

Aldrichimica Acta replaces the previously published *Kardindex Sheets* to keep chemists informed of the latest chemical offerings by Aldrich Chemical Company, Inc. The articles also published are of general interest to users of chemicals and Aldrich customers. While the information and data included in this publication is correct and reliable to the best of our knowledge, it is not guaranteed to be so. Therefore, we cannot assume responsibility connected with the use of our chemicals or data. The information on or sale of any material is not intended as a license to operate under, or a recommendation to infringe, any patent covering any material or use.

Squaric acid and the aromatic oxocarbons

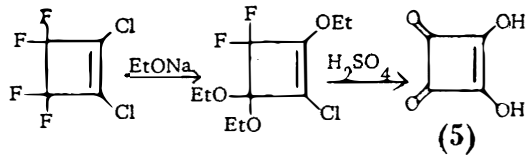
Robert West: Professor of Chemistry, University of Wisconsin, Madison

What was the first aromatic substance ever isolated? Most chemists will guess that the answer is "benzene," and the textbooks agree, crediting Michael Faraday's isolation of benzene from coal tar in 1825. But benzene must share honors with at least one other aromatic compound, dipotassium croconate, isolated in the same year. Moreover, we now know that the croconate ion (2) is merely one member of a series of aromatic anions, the *oxocarbons* (Figure 1). The aromatic nature of these species remained undetected for over a century and has come to light only quite recently.

In the 1820's Berzelius, who was studying the reduction of potassium hydroxide to potassium with carbon, noted the formation of a black solid byproduct. Gmelin investigated this black material and found that in water it gave a yellow potassium salt. From this he obtained an acid which he called croconic acid (from the Greek *krokos*, yellow). Croconic acid was later found to be a cyclic compound having the formula $H_2C_5O_5$, but its real significance remained obscure.*

The story picks up again in 1958, halfway around the world in Japan, where a young undergraduate, Kenichi Yamada, was restudying the croconates as his bachelor's thesis research. Yamada and his mentor, Prof. Y. Hirata of Nagoya University, made the inspired suggestion that croconate ion might have a symmetrical delocalized structure. But their idea did not attract wide attention at the time.

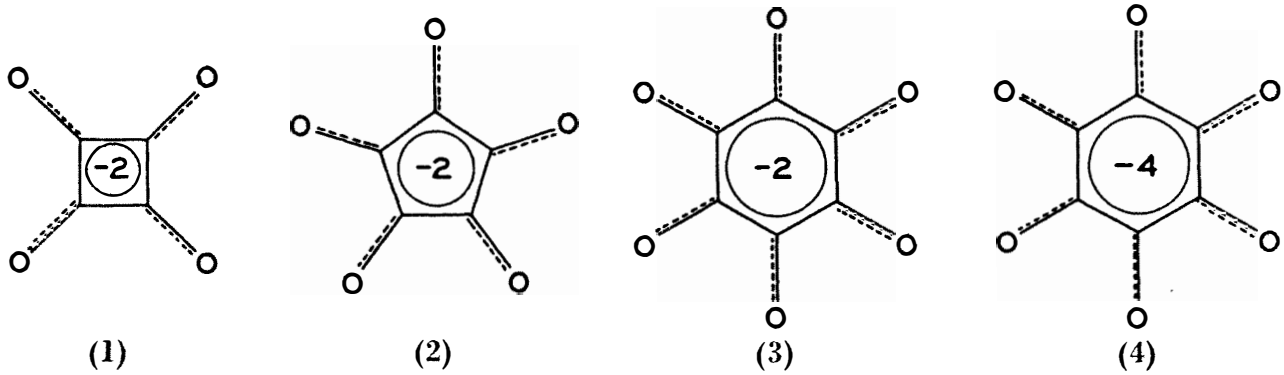
A year later, Cohen. Lacher and Park at the University of Colorado unexpectedly isolated diketocyclobutenediol (5), now better known by the trivial name "squaric acid." Their synthesis was a two-step complete hydrolysis of a dichlorotetrafluororcyclobutene:



(5)

Squaric acid is a stable, colorless crystalline solid, soluble in water but insoluble in most organic solvents. As an acid it is remarkably strong, having dissociation constants about equal to those for sulfuric acid. The Colorado workers suggested that the dianion of squaric acid had a symmetrical, resonance stabilized structure, and their report excited our interest at Wisconsin, for it seemed to us that $C_4O_4^{-2}$ and its homologs $C_nO_n^{-2}$ should be aromatic. We immediately initiated studies of vibrational spectra of the oxocarbon

*Croconic acid has historical importance in quite another connection, for it is now known to be a bacterial metabolic product. It was therefore one of the very first natural products to be synthesized from inorganic materials. The classic synthesis of urea by Wöhler was not carried out until 1828, three years after Gmelin's first publication on the croconates.



(1) (2) (3) (4)

Fig. 1. The oxocarbon anions: squarate (1), croconate (2), rhodizonate (3) and the tetraanion of tetrahydroxyquinone (4).

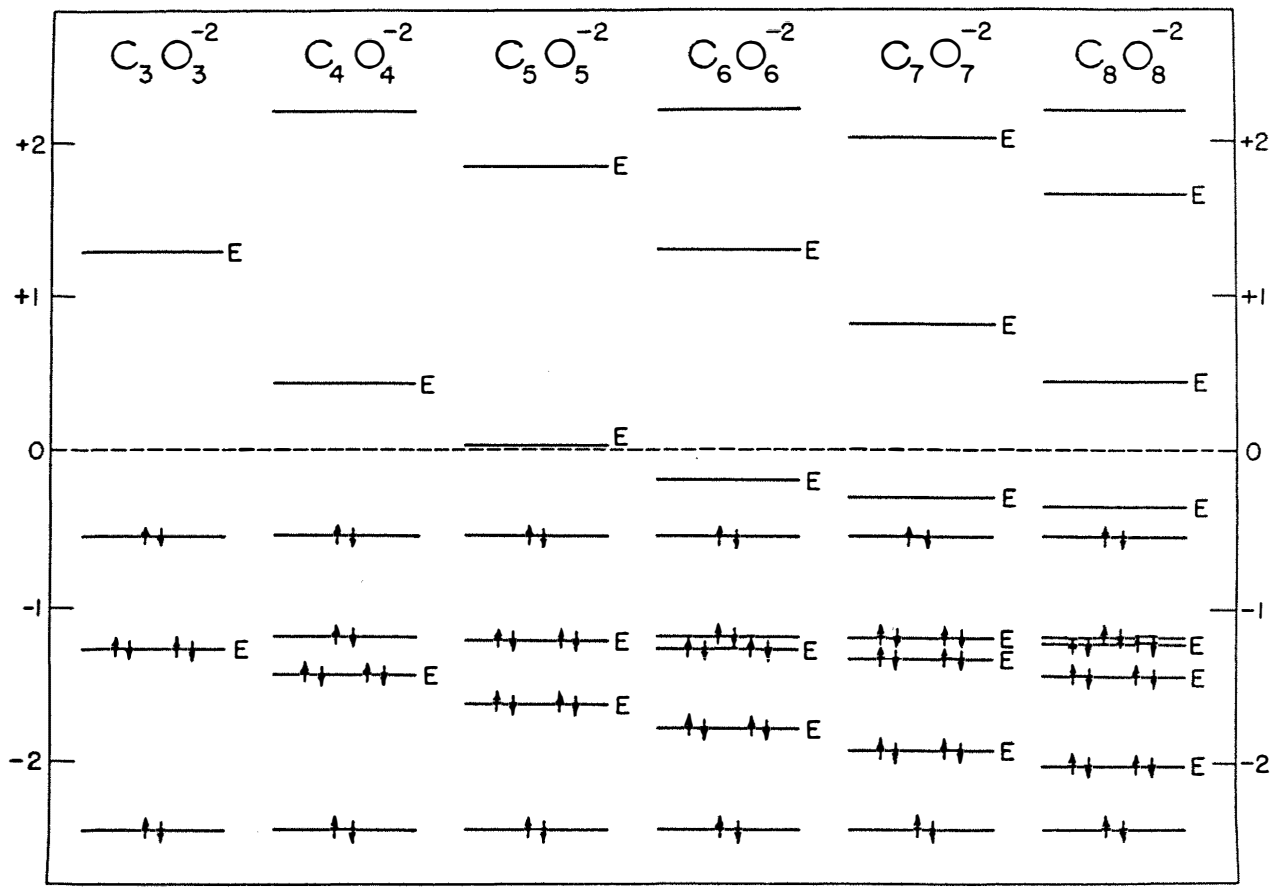


Fig. 2. Pi-electron energy levels from M.O. calculations for the oxocarbon anions $C_nO_n^{-2}$. Electrons are indicated by arrows; the energy levels marked "E" are degenerate and can accommodate four electrons.

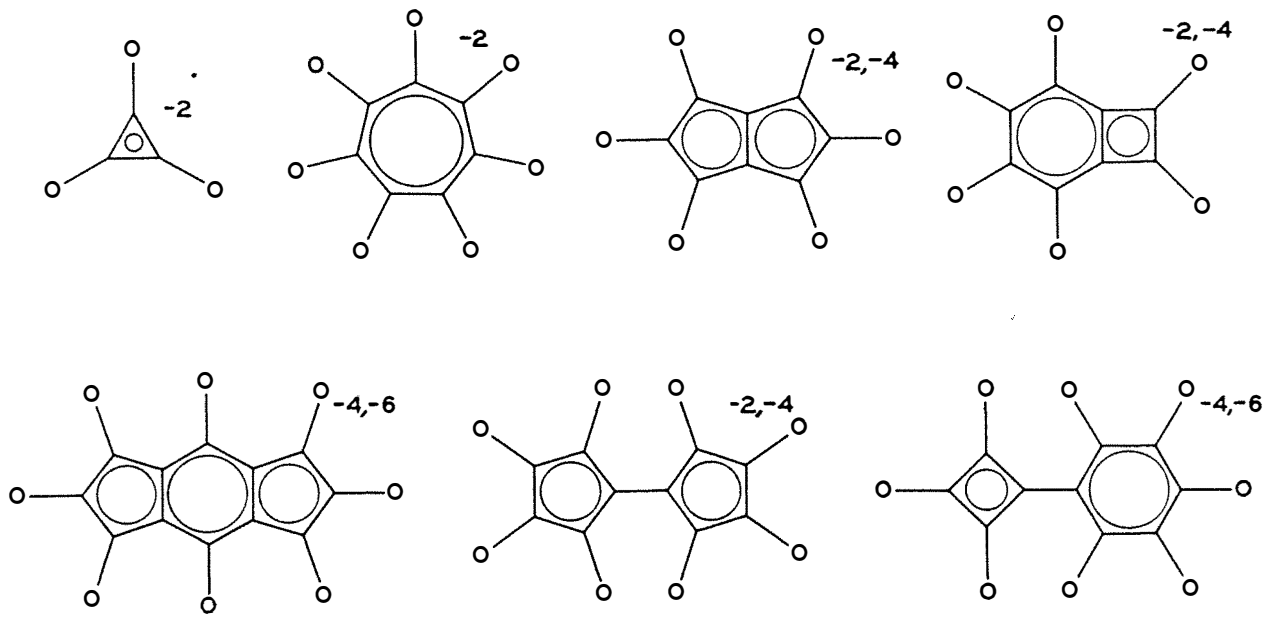


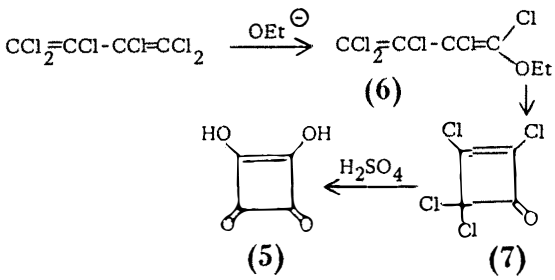
Fig. 3. Schematic structures of unknown oxocarbon anions, predicted to be stable by molecular orbital calculations.

salts, which established the symmetrical planar structures of the anions and led to the recognition of the oxocarbons as an aromatic series.* Aromatic structures for these ions have since been confirmed by X-ray crystallographic studies in several laboratories.

The high symmetry of the oxocarbon anions makes them especially suitable for both structural investigation and theoretical studies, and simple molecular orbital calculations were soon carried out. Results of the M.O. calculations can be assembled as a series of energy level diagrams, shown as Figure 2. Looking at these we were struck by the fact that the lowest-energy unfilled orbital in the dianions is predicted to fall in energy as ring size increases and to become weakly *bonding* for rings with six or more carbons. These calculations led to the successful synthesis of the first oxocarbon anion with –4 charge. $C_6O_6^{-4}$. The M.O. calculations also predict, incorrectly, that $C_6O_6^{-4}$ will be a diradical, reminding us that even now theoretical predictions must still be checked by experiment. But with this exception, the properties of oxocarbon anions agree remarkably well with predictions from simple M.O. theory.

It is interesting that alternation of aromatic stabilization with ring size, as found for the cyclic polyenes, is neither predicted nor observed for oxocarbons. M.O. calculations suggest that *all* of the planar species $C_nO_n^{-2}$ will be aromatic and have high resonance energies. Attempts to synthesize the unknown $C_3O_3^{-2}$ and $C_7O_7^{-2}$ are underway. Moreover, calculations have been carried out on a wide variety of fused-ring and biaryl-type oxocarbons, also expected to be stable, delocalized species. Some examples all presently unknown, are shown in Figure 3.

Squaric acid can now be synthesized more easily by means of a reaction discovered by Maahs. Hexachlorobutadiene undergoes nucleophilic attack by ethoxide ion to give a monoethoxy derivative (6), which condenses thermally or catalytically to tetrachlorocyclobutenone, (7). The latter can be hydrolyzed to squaric acid:

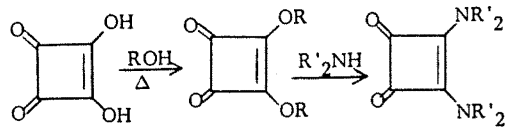


Both squaric acid and tetrachlorocyclobutenone are now available from Aldrich. (Squaric acid appears under the more cumbersome name of 3,4-Dihydroxy-3-cyclobutene-1,2-dione, Cat. No. 12,344-7, and (7) is listed as Perchloro-2-cyclobutene-1-one, Cat. No. 12,343-9).

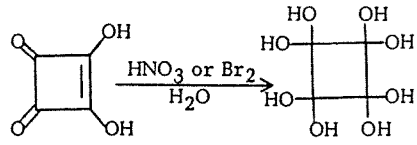
The availability of this unusual compound, squaric acid, has led several groups to study its reactions. Esters of squaric acid can be synthesized simply by refluxing with an alcohol, the squaric acid serving as its own acid catalyst.

*Although our initial work on the oxocarbons was supported by a grant from the Air Force Office of Scientific Research, it is *not* true that we suggested renaming croconic acid as "pentagonic acid".

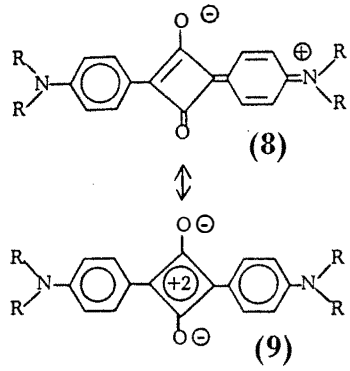
With amines, the esters are converted to amides of squaric acid:



Careful oxidation converts squaric acid to octahydroxycyclobutane:

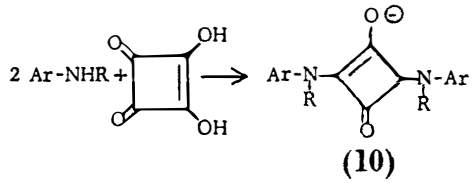


Reactive aromatic and heterocyclic molecules will condense with squaric acid to give a remarkable series of highly colored cyanine-like dyes. For instance, N,N-dialkylanilines give red-violet products formulated as cyanines (8) or possibly better as cyclobutadienylium derivatives (9):

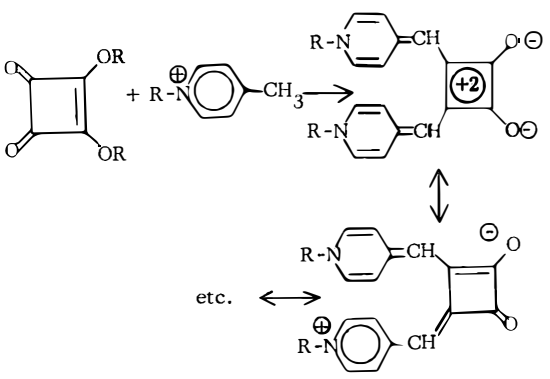


Both (8) and (9) are canonical structures contributing along with other structures to the same resonance hybrid. Which structure is the most important contributor is an unsettled question, now under investigation.

Similar dyes are obtained by condensing squaric acid with pyrroles, azulenes, phloroglucinol, indoles and the betaine bases of quinolinium and benzothiazolium iodides. However, primary and secondary aromatic amines react quite differently, becoming attached to the four-membered ring through nitrogen rather than carbon to give yellow betaine compounds (10):

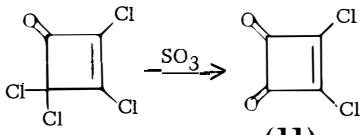


Squarate esters also undergo condensation reactions, for instance with 4-methylpyridinium iodides, but to give 1,2 rather than 1,3 di-substituted products:



The products in these reactions are also intensely colored and may find use as dyestuffs.

Finally, tetrachlorocyclobutenone can be converted with SO_3 to dichlorocyclobutenedione, or "squaryl dichloride" (**11**):

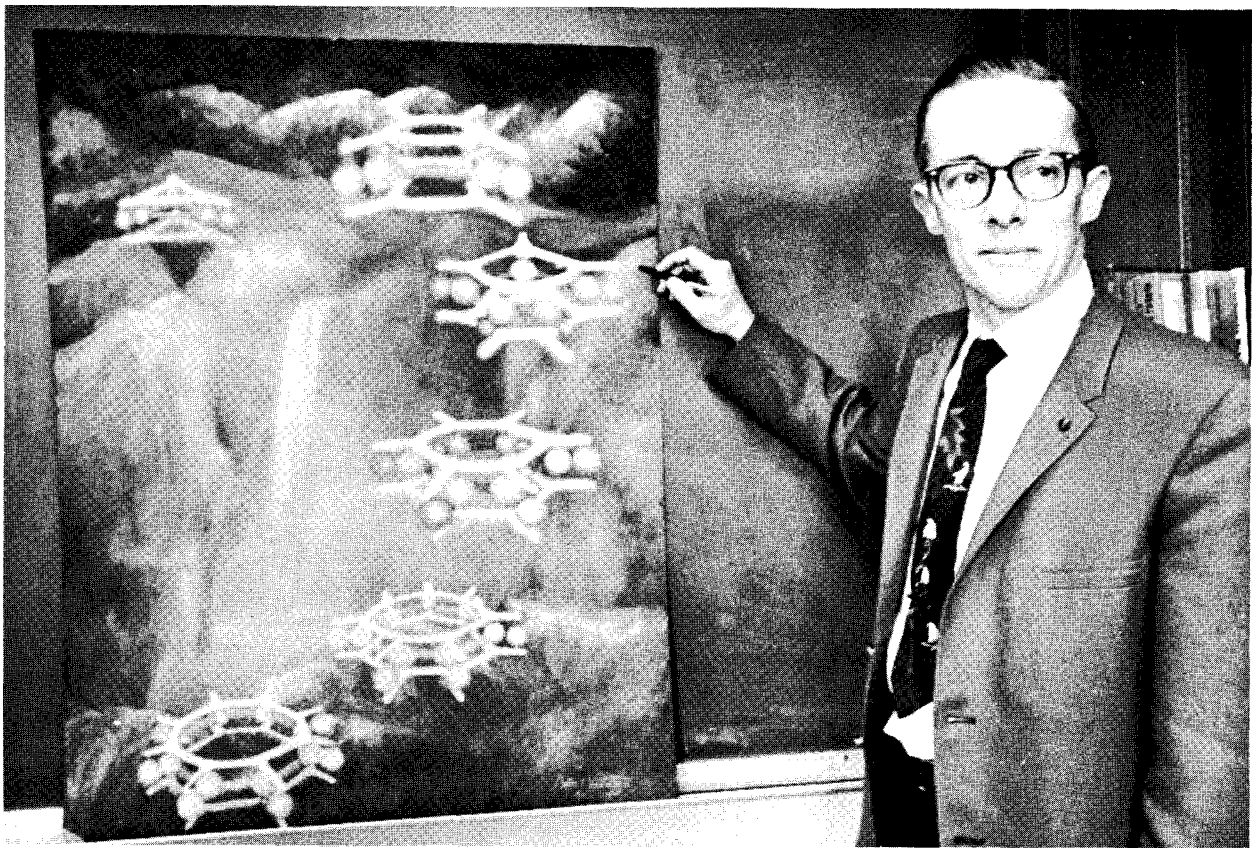


(11)

The latter compound shows the high reactivity typical of an acid chloride, forming esters with alcohols, amides with amines, etc.

Although the aromatic nature of the oxocarbon anions is now relatively well established, only a few of the possible structures are known, and the chemistry of derivatives of the oxocarbons is just beginning. It is likely that the future will see synthesis both of new examples of stable oxocarbon anions and of new kinds of derivatives with unusual electronic properties. The oxocarbon field provides enough possibilities to keep organic chemists busy for years to come.

Additional information about the oxocarbons can be found in a general paper by R. West and D. L. Powell, *J. Am. Chem. Soc.*, 85, 2577 (1963), and in the papers immediately following. Oxocarbon chemistry will be reviewed in a chapter by Prof. West and Dr. Joseph Niu in the forthcoming book *The Chemistry of the Carbonyl Group*, Vol. II, J. Zabicky, editor (Interscience). The chemistry of squaric acid and its derivatives is the subject of a review by G. Maahs and P. Hegenberg, *Angew. Chem. Int. Ed. Engl.*, 5, 888 (1966).



Professor Robert West with his original oil of The Aromatic Oxocarbons *painted by Delbert Venerable of the University of Chicago.*

Of things to come

Alfred Bader: Aldrich Chemical Company, Inc.

The most common question I am asked by friends, customers and stockholders—in fact almost invariably by anyone who discusses Aldrich with me for any length of time, is, "What will Aldrich be doing five or ten years from now?" This may seem like a simple question, and yet, could I have foreseen in 1958 or even in 1963 what we are like today? And why should our crystal ball be clearer now than then?

Nonetheless, a clear knowledge of what has happened in the fine chemical industry generally, and with Aldrich in particular, should allow us to make at least some intelligent guesses of what both will be like ten years from now.

Two fundamental changes have taken place in our industry in the last twenty years; a third is just taking place.

When I was a graduate student at Harvard in the forties, we looked into one catalog to see whether a required research chemical was available. If it was not, we made it ourselves. This catalog has remained essentially unchanged in format and size for the last twenty years. Today, however, several catalogs, American and European, offer many more chemicals, and the Aldrich catalog, listing our products not only alphabetically but also with structures and by classes of compounds and empirical formulae, makes finding a compound or class of compounds much easier.

The second fundamental change has been with purity of the compounds offered. Even only a few years ago, you could not be certain that a given chemical, particularly a liquid, in any of the standard catalogs, was pure. I venture a guess that as many as 30 or 40% of the liquids offered, while having reasonably close boiling ranges, were less than 90% pure, and a fair number would have had v.p.c.'s like Christmas trees. My old friend, Michael Carroll, the discoverer of the Carroll Reaction, said to me in 1952—"You will see, Alfred, gas-chromatography will make honest men of many of us." He was right, and gas chromatography, the greatly expanded use of spectroscopy (i.r., u.v., n.m.r.), thin layer chromatography and the scores of specific functional group methods of analysis have enabled our industry to assure high purity products.

The third change is just beginning: it is the impact of the computer on our industry. Not just the impact on inventory control and invoicing but particularly its impact on finding sources for individual products and groups of definite structural characteristics. Suppose that five years ago a medicinal chemist had found that a cyclopropylamine had a very specific pharmacologic action, and he wanted to compare the action of other cyclopropylamines and perhaps of similar cyclobutyl—and cyclopentylamines also. Where could he have gone? He would have looked into the standard catalogs under *cyclopropyl* and he would have contacted chemists who have recently published on such compounds. Then he would have gone to the literature and made analogs himself. Today Aldrich can send him, at no charge, a complete computer print-out of all our cyclopropyl, or cyclobutyl or cyclopentyl compounds among the 14,000 compounds in our two catalogs; and before long we will be able to supply him with a print-out of all the chemicals in these categories available commercially anywhere. Soon, also, all of the compounds in Chemical Abstracts will have been computer coded and our catalog will list the C.A. code numbers of all of our products, so that it will be easy to determine just what has been published on every compound offered.

Just a few years ago, we bought our first building, and the six of us, who are all still with Aldrich, felt a little lost in the cavernous 27,000 square foot building which was ten times as large as the laboratory we had rented previously. Since then, we have added 160 employees, including nine Ph.D.'s among 40 chemists in all, and we are now housed in much larger buildings and in research and production laboratories specially built for our needs. Most of our expansion in the next ten years will probably come in distribution and in production. We are just moving into a much larger warehouse in New Jersey and will probably add warehouses in Washington, D. C. and other parts of the country. We are not likely to go into the large scale production of anything, but will expand our production facilities, rapidly to be able to make up to 25 kilo lots of many more products.

Ten years ago, our Catalog No. 8 was a simple 82-page compilation of our products listed alphabetically and by classes of compounds only; Catalog No. 9 was the first catalog also to offer compounds with empirical formulae, and Catalog No. 11 with structures. Our Catalog No. 19, ten years from now will probably not look so very different from our present catalog, but our Library of Rare Chemicals catalog will probably list some 25,000 compounds rather than only the 5,000 listed in our present library catalog. Ten years ago we offered only out-of-the-way chemicals; today we also offer several thousand common organic chemicals, and long before 1978 we will undoubtedly have a complete line of every common organic chemical.

The advertisement of Fig. 1, of five years ago, states one of our most important aims: the sale of fine organic chemicals used to support fundamental research. That we have saved chemists throughout the world millions of man hours of labor by supplying chemicals not available elsewhere, is obvious. But Aldrich is today the only major supplier of organic laboratory chemicals whose major—in fact, whose only—business is in organic chemicals, and we have plowed a good share of our earnings back into fundamental research. Five years ago we had made only the modest beginning referred to in the ad. Today we have a Research Department headed by one of the country's foremost medicinal chemists, with some fourteen chemists turning out novel structural classes of chemicals of great significance to both organic and medicinal chemists.

Our dream is coming true.

. . . of things to come !

Oil on copper, 5″ × 5″ Hofstede de Groot No. 240

THE SCHOLAR BY CANDLELIGHT

One of our chemists collects Dutch paintings and managed to pick up a small, early Rembrandt in Vienna some years ago.

Discussing this painting with us, he admitted that he would prefer a late Rembrandt portrait, and yet he almost got us to share his enthusiasm for this small piece of copper. Done in Leiden when Rembrandt was in his early twenties, it clearly foreshadows the great things to come: "The Supper at Emmaus," in the Musée Jacquemart André in Paris; and the "Self-portrait Before the Easel," in Boston, painted only a year or two later.

Perhaps what struck us so forcefully about these comments was their likeness to our own dreams for Aldrich: a modest beginning—a new synthesis of indoles, our work on unsaturated phenols, on o,p'-DDD and cyclohexenones—foreshadowing the things to come: the sale of fine organic chemicals used to support fundamental research.

Figure 1

Available literature

Aldrithiols. Two new thiol reagents, 2, 2′-dithiodipyridine and 4, 4′-dithiodipyridine, are now available from stock. They are excellent reagents for estimation of thiol groups as these reagents can be used over a wider pH range than Ellman's reagent. See sample Kardindex cards below.
Product No. 14,304-9

Bis-(trimethylsilyl)-acetamide (BSA), is an excellent silylating agent for the rapid quantitative conversion of high-melting solids to volatile liquids prior to analysis by v.p.c. BSA is also used as a fast-acting quenching agent for active hydrogen compounds and as a reactant in a novel esterification procedure.
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Diazald®, N-methyl-N-nitroso-p-toluenesulfonamide is one of the most useful reagents developed for the preparation of diazomethane. For detailed procedures and technical literature references, ask for Product No. D2800-0 data sheet.

Glyoxalbis-(o-hydroxyanil) is a useful tool for the quantitative determination of Calcium (II). Extensive literature references.
Product No. G1040-7

Hexamethylphosphorous triamide is the reagent of choice for the preparation of epoxides from aldehydes.
Product No. 14,355-3

3-Hydroxypyridine. Its greatest use is in the synthesis of many types of drugs. Four important derivatives are also available and described with literature references. Recently, some derivatives of 3-hydroxypyridine have been found to function as protective agents of deoxyribonucleic acid (DNA) which has been irradiated with X-rays.
Product No. H5700-9

Iminostilbene is a versatile starting material for the synthesis of many new therapeutic agents.
Product No. 14,365-0

Salicylic acids. A series of new substituted salicylic acids that are of special interest to medicinal chemists. Ask for our listing of these exciting chemicals.

Squaric acid. Please see the feature article written by Professor Robert West that appears on page three of this issue.
Product No. 12,344-7

Tetrachlorocyclopropene is an interesting intermediate in the preparation of two new series of compounds—*triquinocyclopropanes* and *diquinoethylenes.*
Product No. 14,594-7

2, 2, 2-Trichloroethyl chloroformate is an excellent protecting agent for both aliphatic and aromatic hydroxy and amino groups.
Product No. 14,207-7

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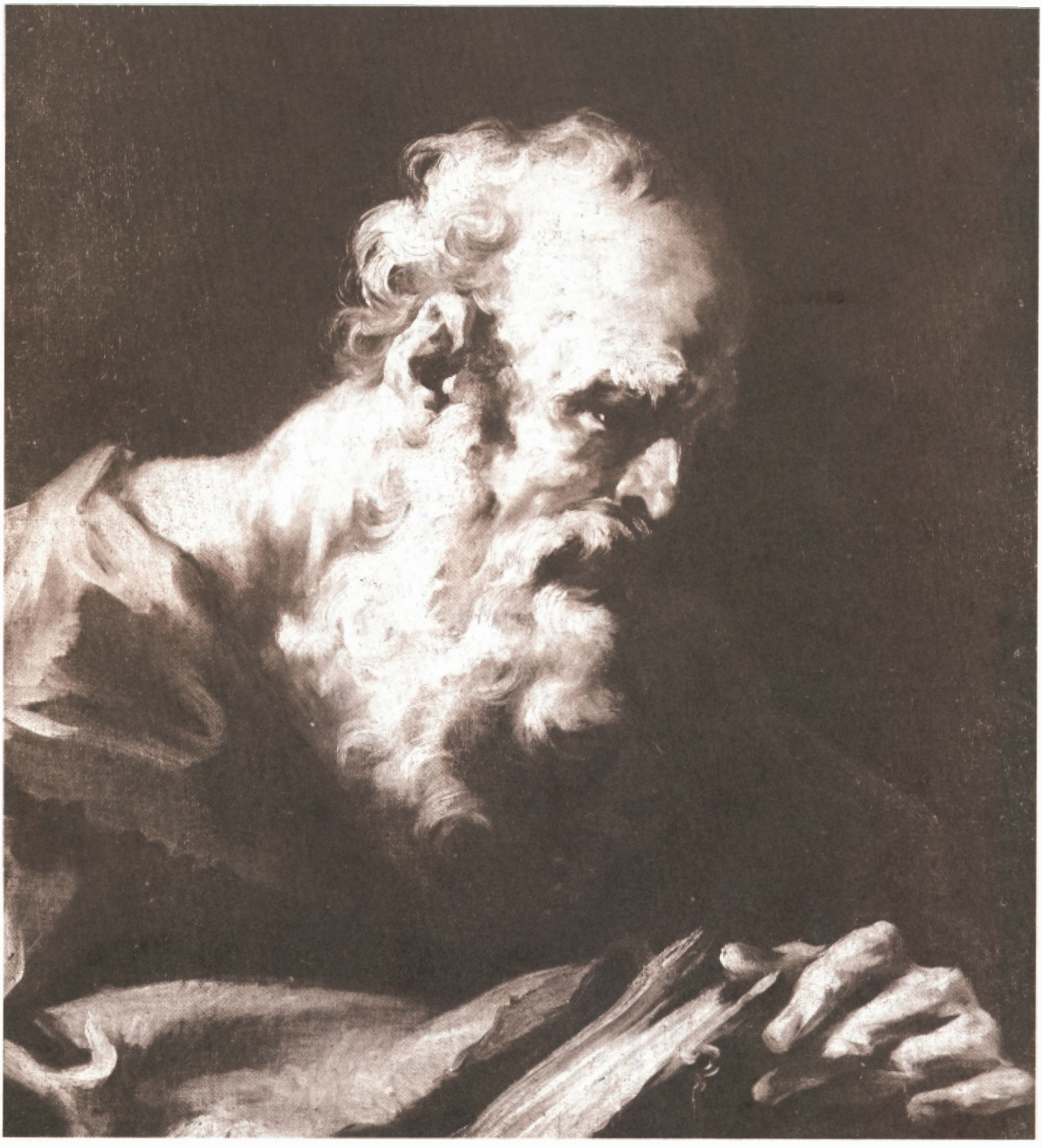
Aldrichimica acta

Volume 1, Number 3, 1968



PUBLISHED BY THE ALDRICH CHEMICAL COMPANY, INC.

ABOUT THE COVER

Our chemist who collects old master paintings is widening his interests: ten or fifteen years ago he looked only for Dutch 17th Century paintings; now he even acquires paintings of which he does not know when or where they were painted. Such is the case with the Head of a Prophet reproduced on our cover.

As our collector explains it, he was minding his own business late one afternoon in Copenhagen, after a busy day discussing chemistry with Niels Clauson-Kaas, one of Denmark's ablest chemists, when he saw this painting in a small gallery, where it had just come from the family of Gauguin, the great painter. Neither Gauguin nor the gallery-owner had any attribution. Nonetheless, our chemist bought this, and the first night could not sleep—haunted by the intensity of this painting beside his bed—Ezekiel in the Valley of Dry Bones.

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ALDRICHIMICA ACTA

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1968

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Editor, Kathleen D. Ryan

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Telephone: 201-539-9494

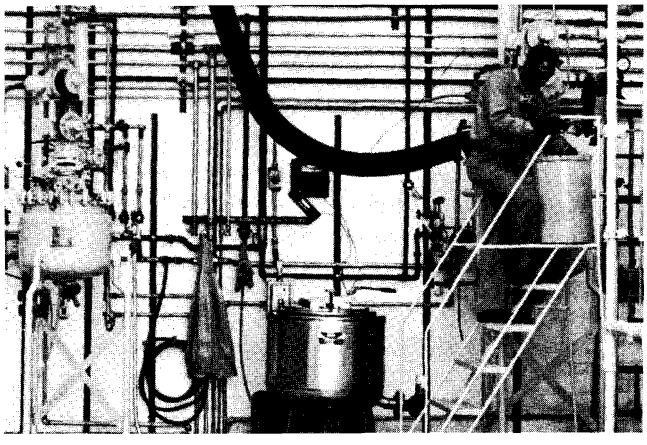
West Coast Distributor:
Wilshire Chemical Co., Inc.,
15324 S. Broadway, Gardena, California 90247
Telephone—(213)-323-9232

The Compleat Chemists

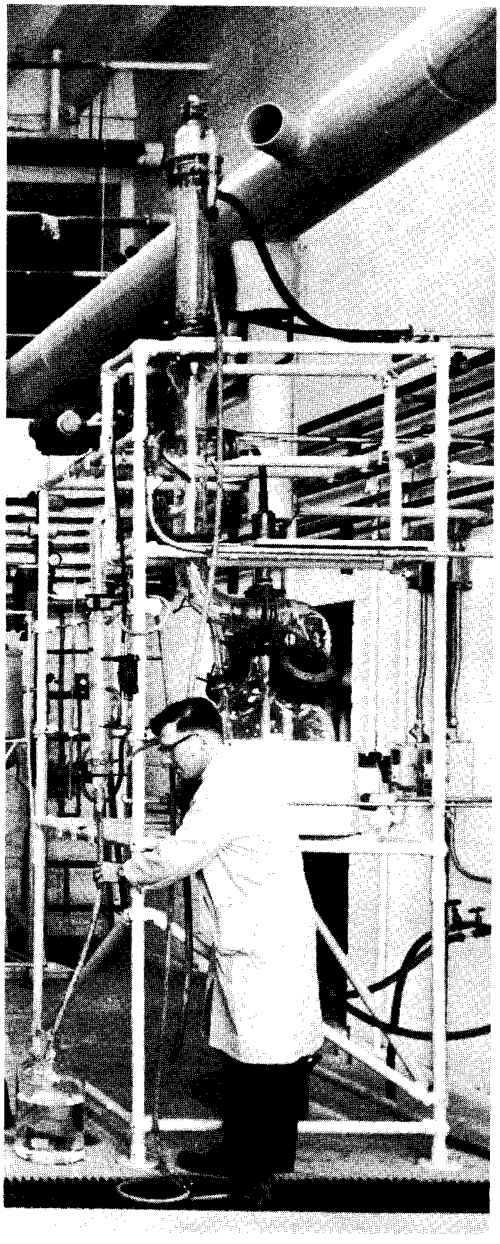
Henry Koppel: Aldrich Chemical Company, Inc.

The first compound offered by us, MNNG, which has since been found to be the most potent mutagenic agent known, was made in a small garage, Aldrich's first quarters. So were the next twelve compounds which we added to our list. Then, however, we began to concentrate on purchasing from Europe interesting organics not commercially available in the United States—until we were challenged with requests for chemicals we couldn't find. These challenges were the beginning of our Production Division. Today it enjoys a completely new laboratory which synthesizes 1000 of the over 9000 chemicals offered in our catalog.

In planning for our move, we reviewed our philosophy of introducing new products and discovered that there were only three limits set by management: 1. The chemical had to have a use and a market potential. 2. It had to be reasonably stable. 3. There had to be a chance that it could be made profitably. Our own curiosity and interests are stimulated primarily by two outside sources. Current technical literature in the journals gives us many clues as to the major directions of research and likely compounds that will come into greater use. Our daily mail brings many requests from all over the world for custom synthesis of many interesting compounds. Many such chemicals, tert.-butoxycarbonyl azide, BSA, and acryloyl chloride, to mention just three, have since become regular production items listed in our catalog. At any one time there are usually twenty or thirty compounds under investigation. At least twelve new items are added to our catalog each month.

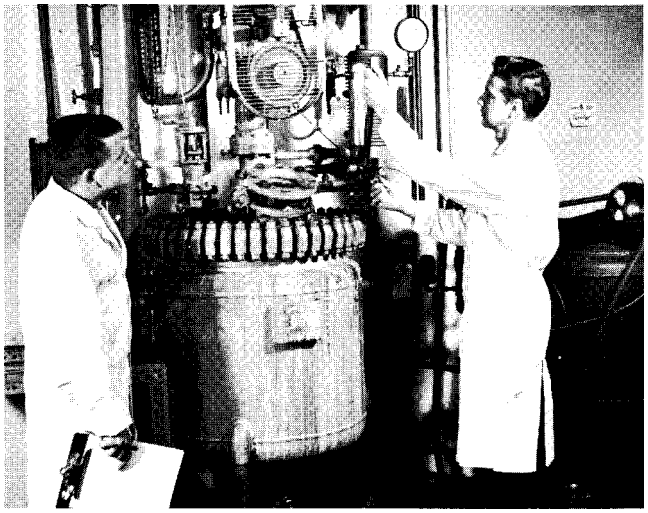


Product from the Pfaudler ready for the centrifuge.



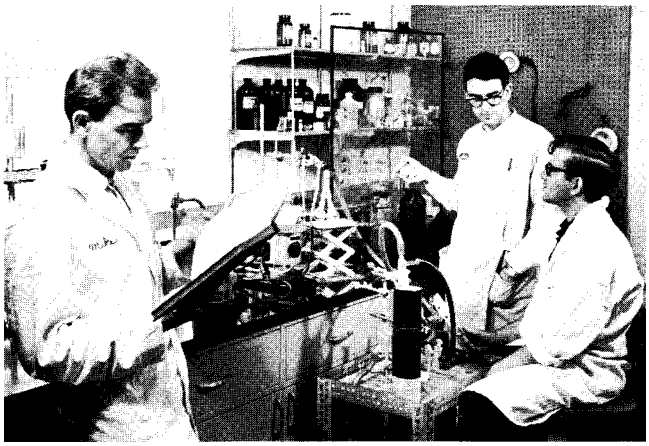
Solvent distillation using Corning glass plant.

One problem faced by all companies in the fine organic field is how to plan facilities to make many different chemicals (in our case, over one thousand) whose yearly sale may range from 100 grams at a high price (a prime example is our cinnoline at $12.00 per gram) to three to four hundred kilos of a relatively inexpensive chemical (such as our Diazald® at $35.00 a kilo in 10-kilo lots). The answer, we feel, lies in flexibility. First, our chemists must be



Checking 50 gallon Pfaudler

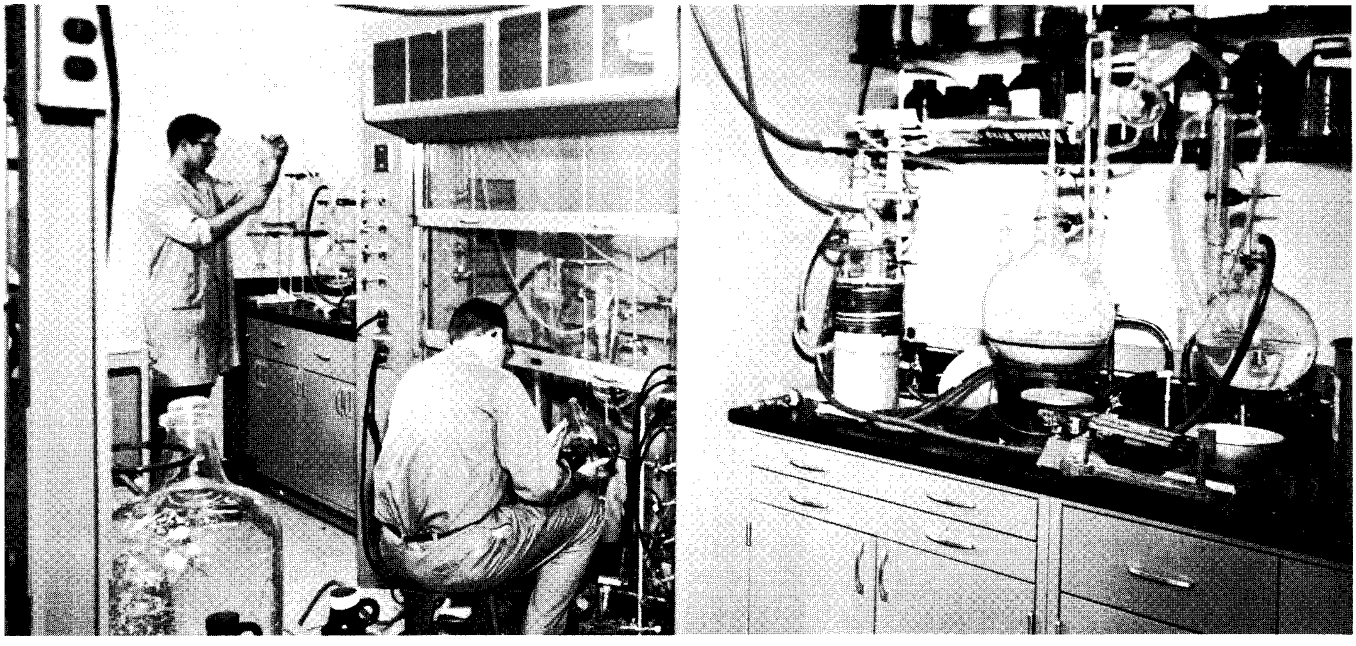
flexible. All our bench chemists have at least a nodding acquaintance with our pilot plant and may be called upon to help scale up a reaction from the 100-gram stage to the multi-kilogram level. Secondly, the equipment must be extremely flexible. Each new piece of equipment whose



Discussion regarding vacuum distillation.

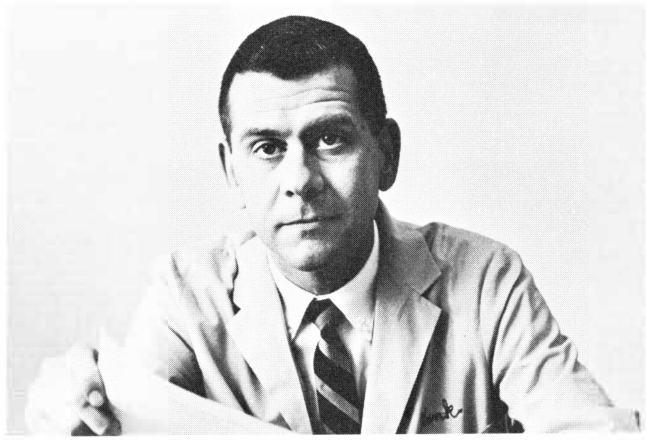
purchase is being contemplated is rated as to flexibility as to how many products it can be used for. We really cannot afford to tie ourselves down to a piece of equipment, no matter how excellent, if its function is limited to one or two processes. This rules out the highly automated process equipment that large chemical manufacturers find useful, and opens the door to improvisations. It would embarrass me to write down the times during the last year that we have run a beautiful reaction in our $5,000 plus Corning glass plant only to work it up in a $4.98 Sears and Roebuck garbage can.

We have accordingly planned our new quarters to be as flexible as possible. Small scale bench work is done in modern efficient two-man labs. The laboratories are air-conditioned, and all plumbing drains are made of Pyrex glass to guard against corrosion. For the purpose of checking the course of reactions, our chemists have available to them the usual analytical tools, such as melting point apparatus and refractometer, plus such specialized items as infrared and v.p.c. These analytical checks in no way take



Various reactions in a typical two man laboratory. The scale here is from very small glassware up through twelve liter flasks.

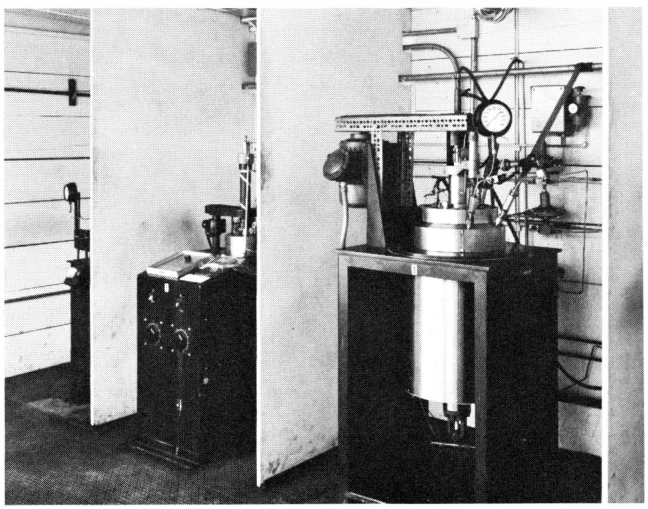
From the centrifuge to the vacuum oven for drying.

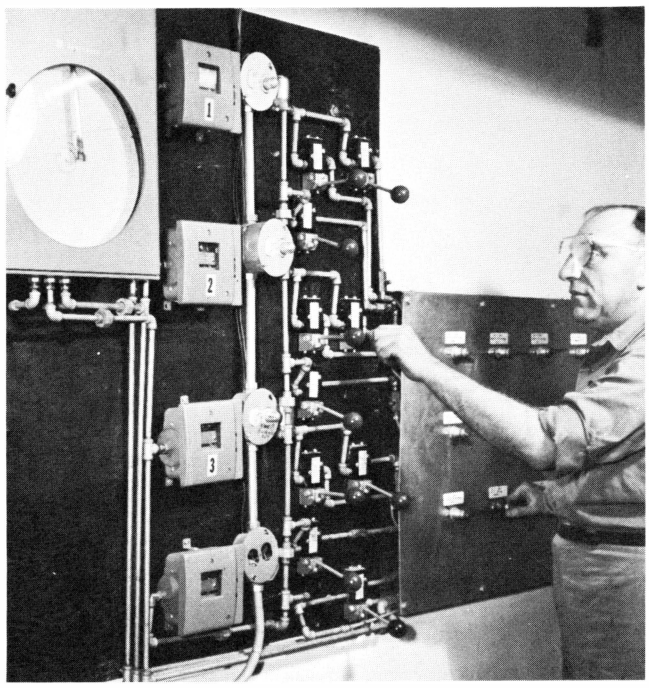


Henry C. Koppel: Director of Production Division.

the place of the rigorous check that all our final products get from our Analytical Control Department. Our larger scale work is done in our pilot plant, which offers us such tools as a Corning glass plant, several Pfaudler glass-lined steel reactors, a ten-gallon resin flask and many assorted 50-liter and 22-liter, round-bottom flasks. For ease and speed of filtration we use a 26″ basket centrifuge; for high-boiling and heat-sensitive liquids, we have found a falling film molecular distilling apparatus a useful piece of equipment. Of the many compounds we produce ourselves many require high pressure hydrogenation. These are produced in our remote-controlled autoclaves. For experimental work we have one 500cc and two one-gallon autoclaves, and for production, a ten-gallon autoclave. All are Magna-Drive autoclaves produced by Autoclave Engineers and can handle pressures up to 4000 psi. The gallon and 10-gallon autoclaves are busy almost around the clock, and we believe that there are few companies of our size with such efficient high-pressure equipment.

Now we find ourselves in beautiful new quarters in an efficient building and look forward to being able to serve our customers in a highly satisfactory manner. If you would like us to list a chemical that is not commercially available, please contact us, and we will give it our careful consideration.



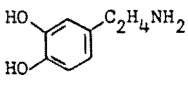


High pressure autoclaves. Pictured is one ten gallon unit and two one gallon units—all of which are operated by remote control for obvious safety factor.

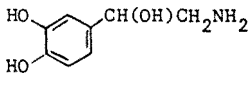
Biogenic Amines and the Emotional State

John H. Biel, Ph.D.: Vice President, Director of Research
Aldrich Chemical Company, Inc.

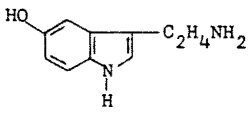
The symposium on "Biogenic Amines" sponsored by the Division of Medicinal Chemistry at the recent San Francisco ACS Meeting explored in depth the role of endogenous biogenic amines in the control of various body functions. These amines were:



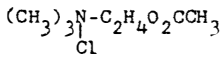
Dopamine



Norepinephrine



Serotonin



Acetylcholine

The principal conclusion which emerged from this conference was that the chemical manipuation of these hormones by the administration of drugs has brought about major advances in the treatment of *mental illness* and *cardiovascular* disease.

It is worthy of note that two such seemingly unrelated disease categories (emotional vs. physical) would yield to similar chemotherapeutic approaches and it emphasizes rather strikingly the intimate relationship between mind and body.

In addition, most of the known hallucinogens with the exception of marijuana embody within their molecular architecture the structural skeletons of dopamine and serotonin, viz.: (Fig. 1).

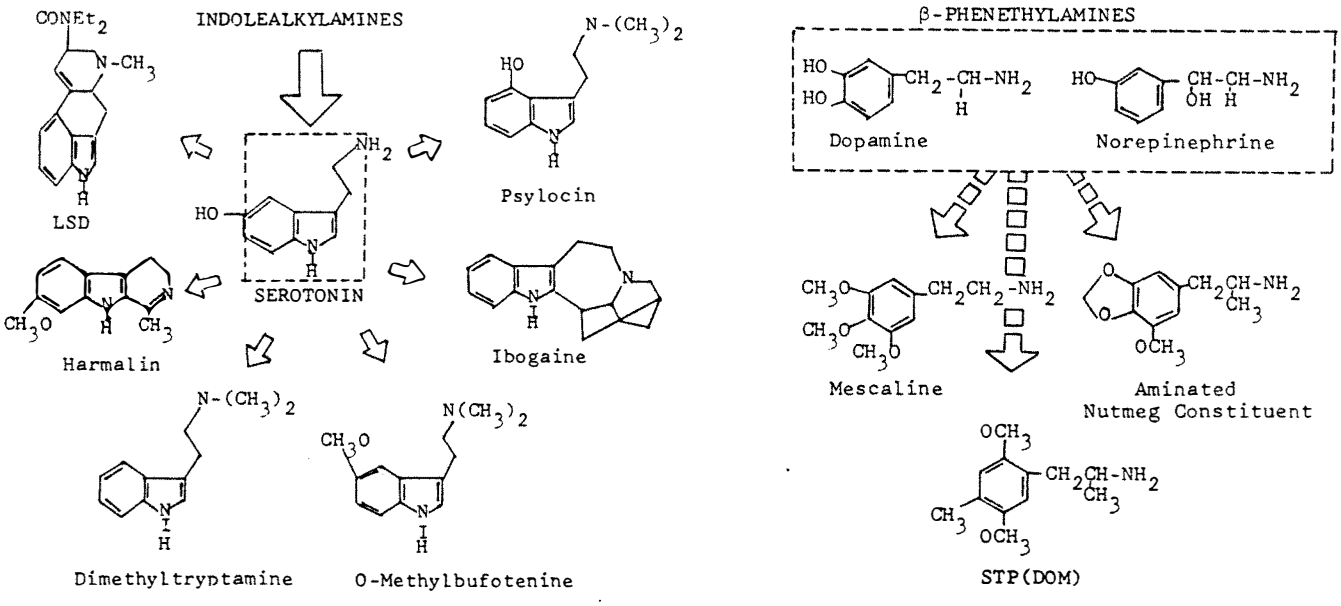


Fig. 1. Structural relationship of the common hallucinogens to the biogenic amines (neurohormones): serotonin, dopamine, and norepinephrine.

Being similar in structure to the endogenous amines, they presumably compete for the same cell receptor sites in the brain and thereby upset the chemical equilibrium in the central nervous system leading ultimately to abnormal behavior patterns.

To understand the mechanism of action of the tranquilizing and antidepressant drugs, it is necessary to know something about the biogenesis of the endogenous amines and factors governing their storage, release, cellular reuptake and metabolism.

BIOSYNTHESIS AND METABOLISM OF NOREPINEPHRINE

Figure 2 depicts the biosynthesis and metabolism of norepinephrine and the chemical tools currently available for blocking some of the biogenic and metabolic pathways.

α-Methyltyrosine (α-MT) blocks the biosynthesis of DOPA and hence, causes a depletion of both dopamine and norepinephrine. This results in sedation in both animals and man. Unfortunately, the drug is too toxic to be of value for therapeutic application. It is a valuable tool, however, in elucidating the mechanism of the central actions of amphetamine. Premedication of the animal with α-MT abolishes all of the central effects of amphetamine. This inhibition is reversed by exogenously administered norepinephrine (NE). Hence, the central stimulant properties of amphetamine are dependent on the availability of freshly synthesized NE.

Pletscher has shown recently that N-1-serinyl-2,3,4-trihydroxybenzylhydrazine (Ro 4-4602/1) blocks the decarboxylation of DOPA to dopamine in the *periphery* of the body. As a result of the peripheral accumulation of DOPA, which can cross the blood brain barrier, *brain* dopamine levels rise significantly, since the DOPA decarboxylase inhibitor (Ro 4-4602/1) is incapable of penetrating brain tissue, and normal decarboxylation can proceed uninhibitedly. It has long been postulated that Parkinsonisms may be associated with a deficiency in brain dopamine. Thus Ro 4-4602/1 offers a possible therapeutic approach to the treatment of Parkinsonism.

Recent experiments by Creveling et al.* suggest a more important role for dopamine as a neurotransmitter of central adrenergic function than heretofore thought. Reserpine-induced depression in animals could not be reversed by administering a metabolic precursor of NE, 3, 4-dihydroxyphenylserine, but was indeed overcome by DOPA, the precursor of dopamine.

*C. R. Creveling, J. Daly, T. Tokuyama, and B. Witkop, Biochem. Pharmacol. 17, 65 (1968).

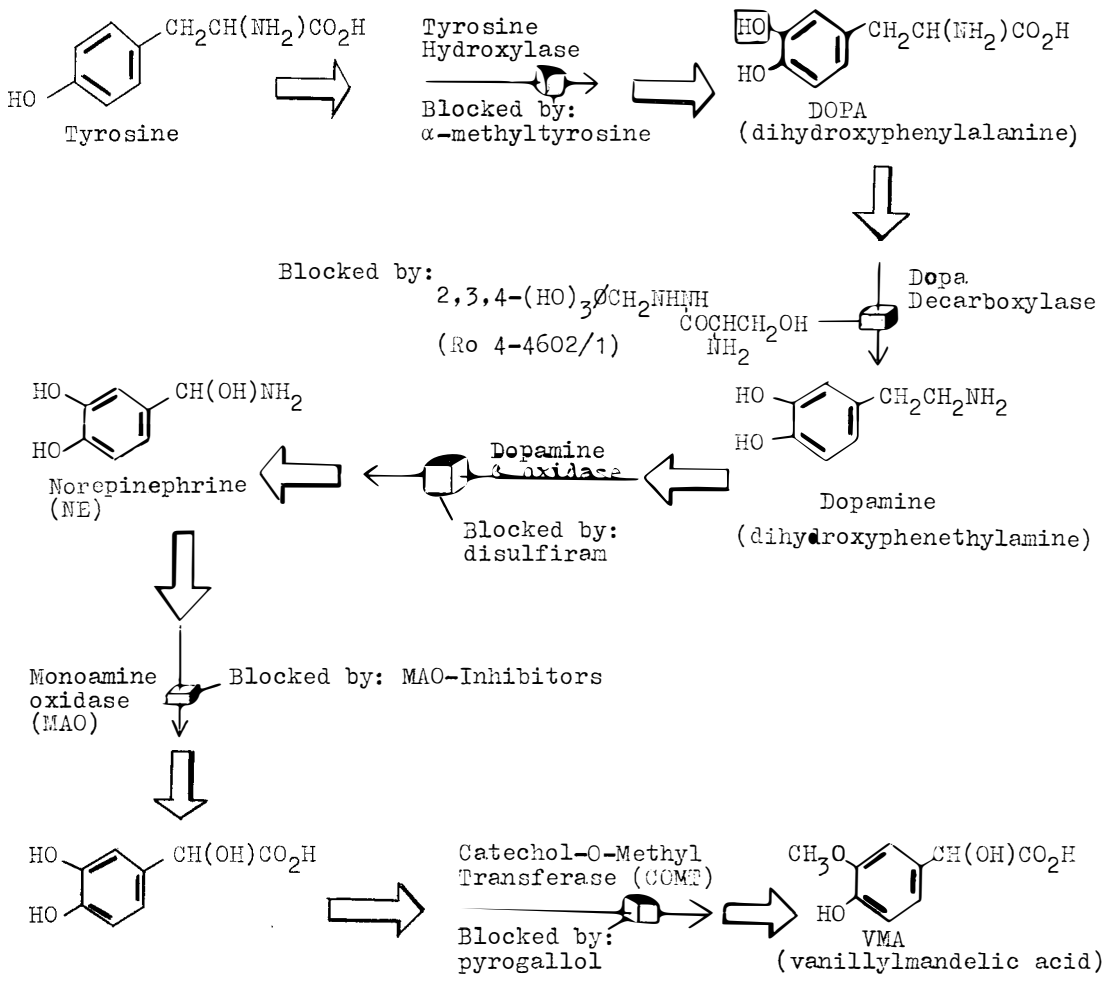


Fig. 2. Biogenic and Metabolic Pathways of Endogenous Catecholamines.

Disulfiram (also known as Antabuse®) which blocks the side chain hydroxylation of dopamine to NE also sensitizes the body to the effects of alcohol. A correlation between these two phenomena has as yet not been established. However, an interesting corollary to this are the studies by Davis et al.* which demonstrate that alcohol will alter the metabolism of NE and epinephrine by sharply decreasing the urinary excretion of VMA and at the same time increasing urinary levels of 3-methoxy-4-hydroxyphenylethyleneglycol (Fig. 3).

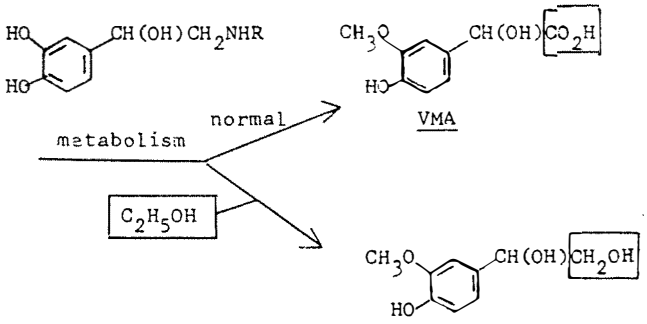


Fig. 3. Alteration in catecholamine metabolism following the ingestion of alcohol in human volunteers.

The authors cautiously speculate that the behavioral changes elicited by alcohol might be related to an accumulation of the "ethyleneglycol" metabolite in the brain.

The inhibition of the oxidative degradation of norepinephrine by MAO inhibitors results in increased brain levels of NE and dopamine. Drugs capable of achieving this effect have found valuable therapeutic application in the treatment of mental depression, suggesting a biochemical basis for the overt symptoms of depressive illness.

CHEMICAL INTERFERENCE WITH CELLULAR STORAGE, RELEASE, AND RE-UPTAKE OF CATECHOLAMINES

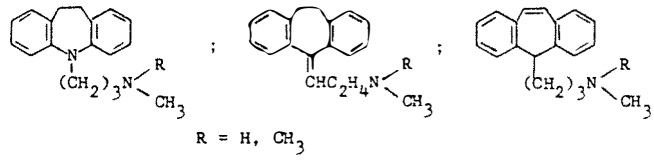
The transmission of adrenergic nerve impulses is dependent on the release of NE and, possibly, dopamine from cellular storage sites onto the adrenergic receptors at the target organ. Once the amine has exerted its stimulant effect it is quickly taken up again by the cell, resulting in the termination of the stimulus (Fig. 4). In other words, as long as the amines are bound to cellular storage sites, they do not exert any pharmacologic effects. Thus, the re-uptake of released (unbound or free) NE or dopamine by the cell represents the main pathway of catecholamine inactivation.

The cellular storage site may be pictured as a pool filled with catecholamines which is kept from "overflowing" by the enzyme MAO (fig. 4.). Inhibition of MAO results in the "spillage" of the transmitter amines onto the adrenergic receptors resulting in heightened central adrenergic responses and antidepressant effects (Fig. 6).

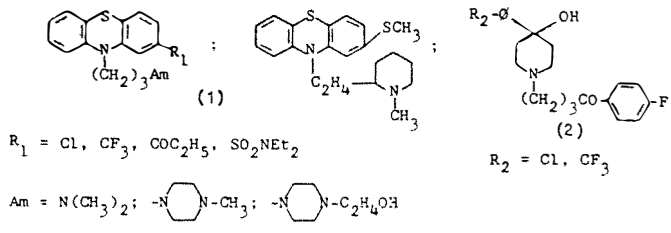
On the other hand, if the storage pool is depleted of its catecholamines by reserpine or certain quinolizine derivatives, which impair cellular binding, central depression and tranquilization result due to the lack of sufficient neurotransmitter amines to interact with adrenergic receptors (Fig. 5). In man, there are reported cases of mental depression following the ingestion of high doses of reserpine.

*V. E. Davis, J. L. Cashaw, J. H. Huff, H. Brown and N. L. Nicholas. Proc. Soc. Exptl. Biol. Med. 125, 1140 (1967).

Compounds which inhibit cellular re-uptake of "released" (free or active) catecholamines and thereby produce increased CA concentrations at adrenergic nerve endings, will achieve a marked activation of the adrenergic nervous system (Fig. 7). As a consequence, these drugs have become the most widely used agents in the treatment of mental depression. Structurally, they are characterized by having a "skewed" (rather than flat) tricyclic ring system with a secondary or tertiary aminoalkyl side chain and generally no ring substituents:



Drugs which compete with catecholamines for central adrenergic receptor sites or block interaction in some other way cause a marked depression of the adrenergic nervous system and produce a tranquilizing and antipsychotic action. The major tranquilizers are either adrenergic or dopaminergic blocking agents. Two principal structural types are available: (1) the phenothiazines and (2) the butyrophenones.



In contrast to the "skewed" dibenzazepine and dibenzocycloheptadiene the phenothiazine moiety is a *flat* tricyclic ring system.

The various biological events referred to above are depicted schematically below:

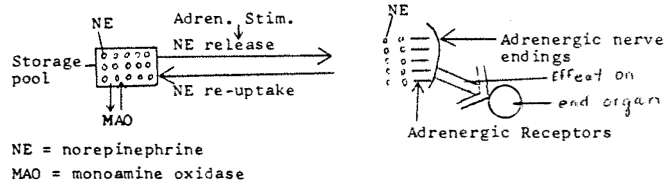


Fig. 4. Normal release and re-uptake of NE after an adrenergic stimulus.

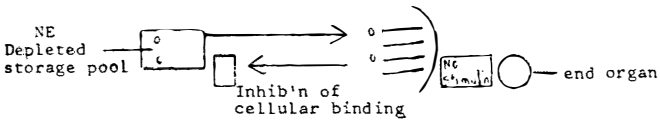


Fig. 5. Effect of reserpine on nerve transmission: Insufficient NE to stimulate end organ.

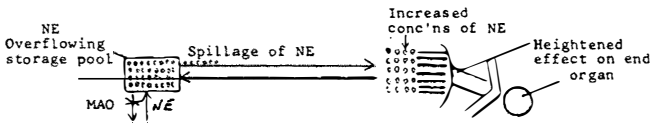


Fig. 6. Increase in adrenergic neurotransmission due to MAO inhibition.

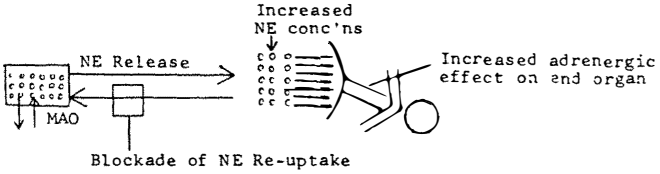
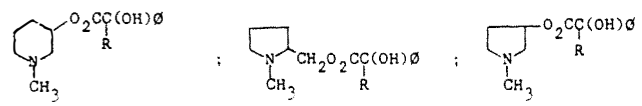


Fig. 7. Increase in adrenergic neurotransmission due to inhibition of cellular re-uptake of NE by tricyclic antidepressants.

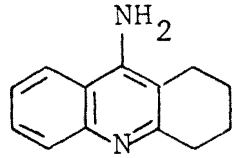
CENTRAL BLOCKADE OF ACETYLCHOLINE

Glycolate esters of hydroxypiperidines and pyrrolidines are powerful inhibitors of the neurotransmitter of the parasympathetic nervous system, acetylcholine. Centrally, these properties are



R = phenyl, cycloalkyl

reflected by the production of bizarre behavior patterns in humans which are often indistinguishable from schizophrenic symptoms. The psychotic reaction to these drugs can last from 8-36 hours and can be reversed almost instantaneously by the injection of a cholinesterase inhibitor (which prevents the hydrolytic cleavage of acetylcholine), tetrahydroaminacrin (THA).



THA

The potent psychotomimetic effects resulting from the central blockade of acetylcholine raise many interesting questions regarding the role of this neurotransmitter in the control of emotional behavior.

SEROTONIN

The role of serotonin in the body still remains obscure. p-Chlorophenylalanine which can block its biosynthesis does not elicit any overt pharmacologic effects. Recently, Carlsson et al.* have postulated that some of the tricyclic antidepressant drugs may act by inhibiting the cellular re-uptake of serotonin in the CNS.

CONCLUSIONS

There is strong circumstantial evidence to suggest that the biogenic amines: dopamine, norepinephrine, acetylcholine and, possibly, serotonin are implicated in the control of brain function and that normal emotional behavior is the result of a sensitive balance of opposing chemical forces in the central nervous system. Mental break-downs may be either the trigger or the reflection of a chemical imbalance. In either situation, the use of tailor-made drugs which have profound effects on these biogenic amines has been successful in alleviating the overt symptoms of many types of psychotic and neurotic behavior.

*A. Carlsson, K. Fuxe, and U. Ungerstedt, J. Pharm. Pharmacol. 20, 150 (1968).

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Aldrichimica acta

Volume 1, Number 4, 1968

PUBLISHED BY THE ALDRICH CHEMICAL COMPANY, INC.

The front cover is discussed on page 15 in Mr. Anthony M. Clark's article on Dutch art and the Aldrich Collection.

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Editor, Kathleen D. Ryan

Chemistry of The Quinuclidines

John H. Biel and E. J. Warawa
Research Division
Aldrich Chemical Company, Inc.

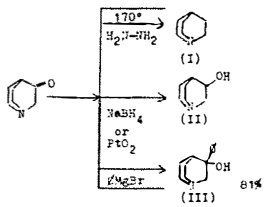
The quinuclidine ring represents a caged heterocyclic ring system with a rigid conformation in which the piperidine ring can only exist in the boat form:

Its unique conformation results in a low steric requirement for the nitrogen atom, making quinuclidine not only a strong base but also one of great nucleophilic character. This structural rigidity coupled with an "exposed" nitrogen confer both interesting chemical and biological properties on its derivatives.

Since 3-quinuclidinone is the most accessible and chemically most versatile intermediate, this discussion will center mainly around the reactions of this interesting heterocyclic aminoketone and some of its key derivatives.

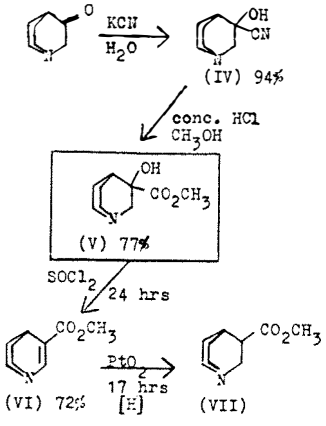
I. CHEMICAL REACTIONS OF 3-QUINUCLIDINONE

(1) *Reductions*[1, 2]



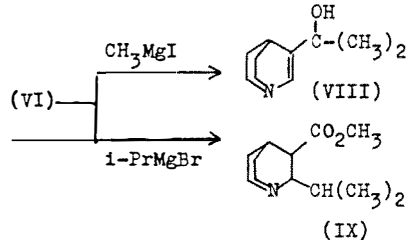
(2) *Carbonyl Addition Reactions*

a. Hydrogen Cyanide Addition and Production of Quinuclidine-3-Carboxylic Acids[3]

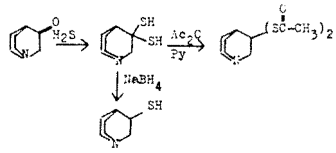


It may be seen that reactions in the 3-position proceed only under rather stringent conditions, such as the dehydration of (V) and the hydrogenation of the α,β-unsaturated ester (VI).

The Grignard reaction of (VI) with methylmagnesium iodide proceeds via a 1,2-addition, while with the bulkier isopropylmagnesium bromide, a 1, 4-adduct is obtained:[2]

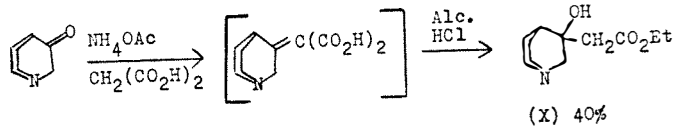


b. Hydrogen Sulfide Addition[4]

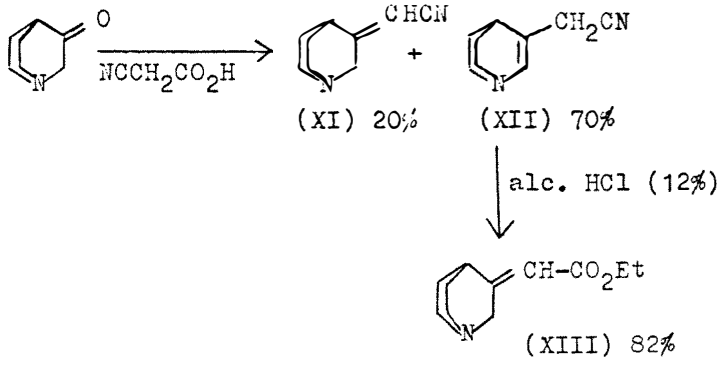


(3) *Knoevenagel Reaction*[5]

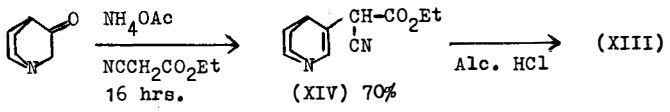
a. With Malonic Acid



b. With α-Cyanoacetic Acid

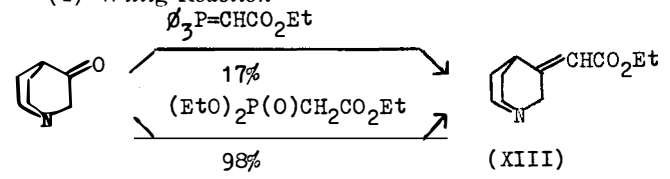


c. With Ethyl Cyanoacetate

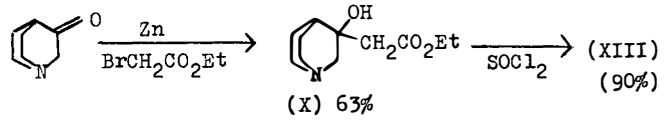


Under acidic conditions, the endocyclic double bond becomes exocyclic with the formation of an α,β-unsaturated acid.

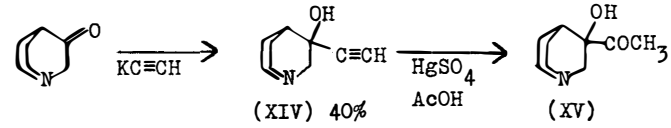
(4) *Wittig Reaction*[6]



(5) *Reformatski Reaction*[7]

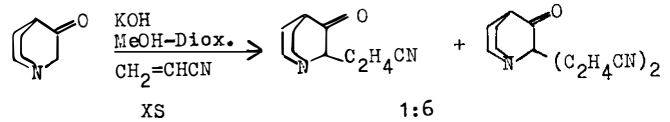


(6) *Reaction with Potassium Acetylide*[2]

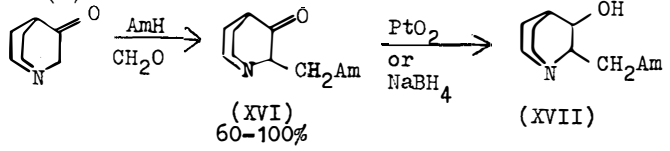


Compound XV did not dehydrate.

(7) *Cyanoethylation*[8]



(8) *Mannich Reaction*[9]

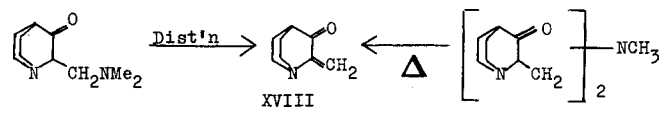


Am = dialkylamino, morpholino, piperidino, 4-methylpiperazino, pyrrolidino, etc.

The aminoketones may be converted readily and in high yield to novel aminoalcohols with PtO_2 in acidic media at 3 atmospheres of hydrogen or with sodium borohydride in methanol.

Conversion of 2-methylene-3-quinuclidinone[9]

In cases where Am represents a low boiling amine moiety, distillation affords a high yield of 2-methylene-3-quinuclidinone:

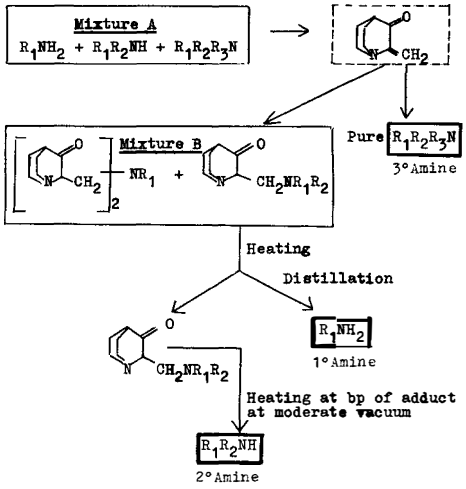


Compound XVIII was also prepared by Nielsen[10] from 3-quinuclidinone and formaldehyde in methanol.

II. 2-METHYLENE-3-QUINUCLIDINONE ITS USE IN THE SEPARATION OF AMINES[11]

The ability of 2-methylene-3-quinuclidinone to add primary and secondary amines and regenerate them again at differential rates (depending on the volatility of the amine) upon heating, makes this reagent a valuable tool for the separation of primary, secondary and tertiary amines as well as other impurities.[11] Adducts obtained from primary amines and 2-methylene-3-quinuclidinone release the amine much more readily than those obtained with secondary amines.

This separation scheme is illustrated below:



The adducts are highly crystalline substances which are readily purified.

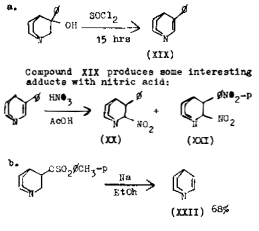
III. REACTIONS OF 3-QUINUCLIDINOL

(1) *Esterification*

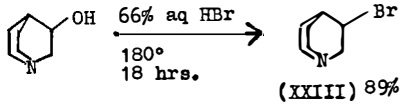
Esters are best formed by ester interchange rather than through the use of acid chlorides due to the high basicity and reactivity of the quinuclidine which often favors the precipitation of a quaternary ammonium addition complex.

(2) *Dehydration*

Rather stringent conditions have to be used to effect dehydration:[2]

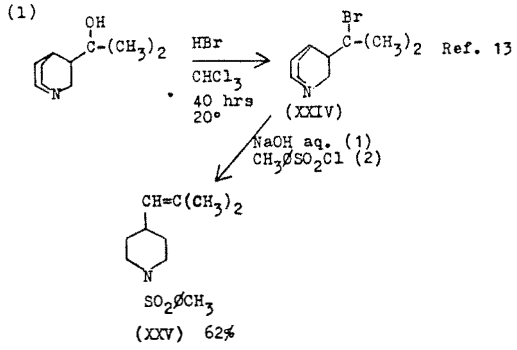


(3) *Bromination*[12]

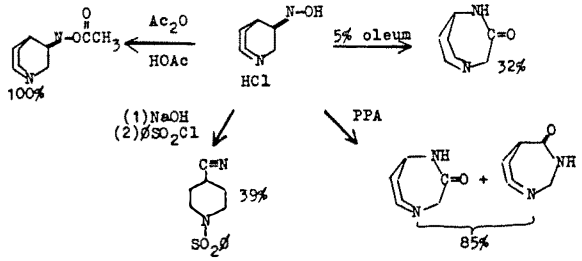


IV. FRAGMENTATION AND REARRANGEMENTS OF QUINUCLIDINE DERIVATIVES

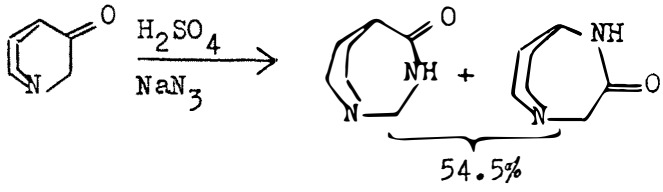
(1)



(2) *Beckmann Rearrangements*[14]



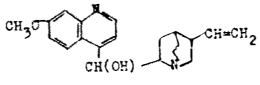
(3) *Schmidt Reaction*[15]



V. BIOLOGICAL PROPERTES OF SOME QUINUCLIDINE DERIVATIVES

(1) *Cinchona Alkaloids*

These naturally occurring quinuclidine derivatives display a variety of antiparasitic and pharmacodynamic properties, as exemplified by quinine, (XXVI),



(XXVI)
quinine

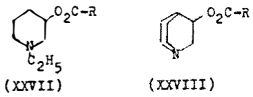
which produces analgetic, antimalarial, antipyretic, muscle relaxant, and oxytocic effects. Its d-isomer (quinidine) is used widely as an anti-arrhythmic agent in cardiac irregularities.

Quinine, one of the first effective antimalarial drugs, fell into disrepute because of its severe side effects when less toxic synthetic drugs became available. However, recently the emergence of drug-resistant malarial strains has brough quinine back into the therapeutic limelight, since it retains its efficacy toward these resistant strains.

(2) *Comparative Biological Properties of Some Quinuclidine and Piperidine Derivatives*

The quinuclidine ring may be considered a piperidine ring with a fixed conformation. This structural rigidity coupled with an "exposed" and, therefore, highly reactive nitrogen would suggest both qualitative and quantitative differences with respect to the biological effects exerted by derivatives of the two ring systems.

a. *Central Nervous System (CNS) and Anticholinergic Properties:* [12, 16, 17]

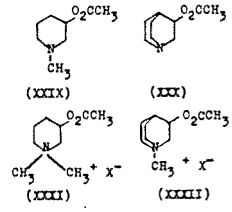


R	Anticholin. Act'y (Atropine = 1)	Anticholin. Act'y (Atropine = 1)
Ø2CH	0.01	1.0*
9-Fluorenyl	0.05	1.0*

*Potent hallucinogenic properties

It may be seen from the above table that the diphenylacetate and 9-fluorenecarboxylate of N-ethyl-3-piperidinol were far less potent anticholinergics than the quinuclidine congeners. Furthermore, the latter are potent hallucinogenic agents in contrast to the two piperidyl esters which are altogether devoid of this action.

b. *Cholinergic Properties of the Acetates*



The quinuclidyl acetate (XXX) is a potent cholinomimetic drug (aceclidine) which is used clinically abroad as a miotic agent (pupillary constrictor) in the treatment of glaucoma. In dogs and cats, 0.1-0.5 mg/kg produced a marked drop in blood pressure which was blocked by atropine.[18] Quaternization (Compound (XXXII) markedly *reduced* cholinergic activity which is totally unexpected on the basis of the structural requirements of acetylcholine which loses all of its potent cholinergic properties as a *tertiary* amino ester.

In contrast, N-methyl-3-piperidyl acetate (XXIX) is devoid of all cholinomimetic properties, while its quaternized derivative (XXXI) displays some cholinergic activity.

Summary

Quinuclidine, a "caged" heterocyclic ring system, undergoes a number of unique chemical reactions which are not always shared by conformationally less rigid congeners. Of particular interest is the chemical scope of 3-quinuclidinone, a now readily available starting material, whose properties are reviewed in some detail.

References

1. E. E. Mikhlina, et al., *Zhur. Obshchei. Khim.*, 31, 2609 (1961); C.A., 56, 11560c.
2. C. A. Grob, et al., *Helv. Chim. Acta*, 40, 2170 (1957).
3. C. A. Grob and E. Renk, ibid., 37, 1689 (1954).
4. K. B. Shaw, *Can. J. Chem.*, 43, 3112 (1964).
5. E. E. Mikhlina and M. V. Rubtsov, *Zhur. Obshchei. Khim.*, 32, 2935 (1962); *C.A.*, 58, 9020f.
6. L. N. Yakhoutov, et al., *Zhur. Obshchei. Khim.*, 33, 3211 (1963); *C.A.*, 60, 4109e.
7. E. E. Mikhlina and M. V. Rubtsov, *Zhur. Obshchei. Khim.*, 30, 2970 (1960); *C.A.*, 55, 18727c.
8. E. E. Mikhlina and M. V. Rubtsov, *Zhur. Obshchei. Khim.*, 29, 118 (1959); *C.A.*, 53, 21953f.
9. A. Hansen and H. Bader, *J. Het. Chem.*, 3, 109 (1966).
10. A. T. Nielsen, *J. Org. Chem.*, 31, 1053 (1966).
11. John H. Biel, Harvey B. Hopps and Henryk Bader, U.S. Patent, 3,384,641 (1968).
12. L. H. Sternbach and S. Kaiser, *J. Amer. Chem. Soc.*, 74, 2215, 2219 (1952).
13. C. A. Grob, et al., *Helv. Chim. Acta*, 45, 1823 (1962).
14. M. V. Rubtsov, et al., *Zhur. Obshchei. Khim.*, 32, 2222 (1964); C.A., 61, 9481c.
15. E. E. Mikhlina and M. V. Rubtsov, *Zhur. Obshchei. Khim.*, 33, 2167 (1963); *C.A.*, 59, 13991h.
16. J. H. Biel, et al., *J. Amer. Chem. Soc.*, 74, 1485 (1952).
17. J. H. Biel, et al., *ibid.*, 77, 2250 (1955).
18. M. D. Mashkovskii and K. A. Zaitseva, *Arzneim. Forsch.*, 18, 320 (1968).

Dutch Art and the Aldrich Collection

Anthony M. Clark
Director, The Minneapolis Institute of Arts.

Address delivered by Mr. Anthony M. Clark at the opening of the Aldrich collection of Dutch Art at the Kalamazoo Institute of Art.

Ladies and Gentlemen:

You might ask why a scholar of 18th Century Italian paintings stands before you at this opening of your Fifth Anniversary Fund Exhibition and has the nerve to speak to you about an art so different from that which he usually studies; as if an expert on desserts and after-dinner mints was to lecture on plain roast beef. Since that is actually what I'm going to do, I hope my natural enthusiasm (and quite natural relief at the momentary change of subject) will carry us along. Also, I'm a museum man who has to look at and use public purchase funds over the wide and catholic range of man's very long and varied artistic creativity, can happily still do this with gusto, and find myself very often brought up short by paintings done in such a number and in such quality in a few decades in that small acreage of the world we call The Lowlands. It is a curious feeling for me—loving and pursuing as I do the grandly framed decorations of Italian palaces and churches, their grand frescoes, huge altars, all that great public art of a bright southern land full of artistic prodigality and emotional generosity—to turn to the private, clear, practical, modest, commonsense skies and landscapes of the Netherlands. For me it is invigorating to do so; not like a cold shower, but like coming home. How wonderful to be able to find enough pleasure in the everyday and the simply good! And that is what the Dutch were able to do. They are remembered not for their grandeur, their private and public splendor, their great buildings and town plans, magnificent gardens or fountains and piazzas, but for a simple form of art with simplest homespun subjects. Their painting, this leading art of theirs, seldom chooses to represent the great gods and heroes, the learned mythological and devotional subjects, and instead presumes to avoid the imaginative world like the plague. A table full of food, a white-washed church with a few solid, common figures, an unpretentious and frank portrait, a street scene, a wild but homespun landscape, poor peasants in a barn, a woman darning a sock, a fancy charade in a farmyard illustrating a Bible story—these were enough for faithful artists of fine technique, and enough for such giants of man's spiritual history as Franz Hals, Vermeer, and Rembrandt.

Although the exciting exhibition you open today shows Dutch *and* Flemish paintings of the 17th century, I am going to restrict my short words to the Dutch art. In this school of painting I believe that the Aldrich Collection is most interested, and the Flemish paintings that they have so well selected for you are, even including the exceptions of the Van Dyck and Cornelius de Vos portraits, those which would have felt most at home in 17th Century Holland. For remember that in the baroque century Flanders was typically a far showier place and, utterly unlike the Dutch, the Flemish began with the superb and academic—let us call it the very worldly and even vulgar (except in the imaginative opulence of a Rubens, a Van Dyck, or a Jordaens, who all had assimilated the grander inventions of Italy), and that the Flemings never approached the striking Dutch achievement unless trained in it and following its lead, as was a painter like Adriaen Brouwer (who can be seen in this exhibition).

What on earth made this Dutch achievement possible? The Republic of the United Netherlands in the 17th century is one of the happier success stories in the heritage of Western history, and one which still is, thank God, almost as familiar as it should be, what with its importance to the Anglo-Saxon tradition of liberty and commerce. Most of Europe in that grandiose century was involved in expensive and complicated wars. Great nation stood against great nation, each paralyzed, as it were, by the glory and greatness of its princely rulers. The Dutch provinces quite literally barely tolerated their ruling House of Orange; proud, free provinces were banded together freely for self-preservation, and the small nation developed a most powerful but egalitarian and unpretentious middle class, and more important, a most sound, natural prosperity. Neutral, and even negligible in the wars of the century, the Dutch became the Banker of Europe and, silently, invisibly, as the others fought, the Dutch surprisingly became the leading sea-power of the world, with most profitable colonies

(Fig. 1)

around the globe. The heroic Dutch navy, the bravery and industry of the Dutch Merchant Fleet, the country's geographical position all provided the most spectacular natural success of the magnificent 17th century. A traditional insistence on decentralization, the good common sense and mercantile liberalism of the ruling class, and a shrewd spirit of tolerance both towards the new and towards minorities, helped transform the prosperity towards that release and breakthrough which we see in Dutch painting, and which is—if in a modest way—really comparable to the extraordinary flowering of Athens and Greece after the Persian wars. The Dutch painting is the happiest and most natural accompaniment to this political and commercial triumph of Holland, which lasted only for a few generations. By the end of the century, power had departed and so, mainly, had the genius of art.

In 1640 a traveler wrote, "As for the art of painting and the affection of the people to pictures, I think none other go beyond them, there having been in this country many excellent men with the faculty and some at present, as Rembrandt, etc. All in general strive to adorn their houses, especially the outer and street room, with costly pieces, butchers and bakers not much inferior in their shops, which are fairly set forth; yea, many times blacksmiths, cobblers, etc., will have some picture or other by their forge or in their stall. Such is the general notion, inclination, and delight that these country natives have to painting." This is an unexaggerated account, and if you will go through a text on Dutch painting you will marvel at the vast number of so-called "minor masters," all of excellent technique and quality, who supplied the demand. The United Provinces took their religion seriously, were not fanatical but tolerated fanatics—think of the radical Protestant sects that began in Holland—but there was one morris dance, one fad, which, if it wasn't so innocent and harmless, could have been called fanaticism, and that was the Dutch love and production of paintings.

It simply can't be explained on much less frivolous grounds than that. And let us remember in passing that the size of the production has much to do with the solidarity and prosperity of the Dutch audience. It is an oversimplifictation to say that 17th Century Dutch painting is the first example of art consumption by a large middle-class audience and is also the grandparent of that ignoble descendant modern television—but there is as much truth in the first of these statements as there is cruel irony in the second of them!

As the century progressed, Amsterdam became the center of the European market, with dealers and auction houses much as there are in London or New York today, a position it held for a century longer. Local trade in the native art was hilariously intense and the single unfortunate lack of Dutch painting is a late 17th Century Daumier whose genre was the art trade as it worked throughout the fancy and low worlds of Holland. But now I'd like to speak for a moment about the collecting of Dutch art, and the beginnings of its great vogue and recognition in the world.

Remember first that since the 14th century the provinces of the Netherlands had a good native share of the fine European painters, and that craftsmanship was always of a very high order. The ancestors of the 17th Century painters were not unworthy primitives—think of Lucas van Leyden and Hieronymus Bosch—amongst the world's very greatest artists, desirable everywhere, world innovators and leaders. These older artists had, incidentally, many of the recognizable artistic virtues that are specifically and inexplicably Dutch—even the familiar Dutch artistic personality was already invented as the 17th century began (just as some of its characteristics can be found in the recent Dutch artists, such as even Van Gogh and the moderns of the Cobra group). The glorious and curious production of the Dutch 17th Century painting was, however, both very special—as brave as Dutch natural and commercial leadership—and different, and even isolated as Holland itself in

the history of the 17th Century European style. Rome and Versailles *are* that style—to put the matter very simply—not Ruisdael or Brouwer, or even Hals, Vermeer, and Rembrandt.

In the first half of the century only those Dutch painters (with their Flemish cousins) who specialized in landscape and genre scenes can be said to have made their mark, by the simple expediency of having gone to Rome and literally invented their two disciplines and art forms in that city where the entire baroque age was invented. The results might be called anti-baroque and oddities of their time, but they were enormously popular and were featured in many grand and ambitious European collections—indeed, they were probably what the great princely owners liked best—more than the huge heroines, etc., of the more famous and honored painters of the day. The Dutch and Flemings became known in all European courts as the only ones who could do certain things: flower pieces, landscapes of great flavor and naturalness, scenes of low life or genre scenes—all usually pictures of informal, small format. The establishment, the leaders of the grander nations had to have these products and even one or two domesticated practitioners of them. They did not, however, buy from the best Dutch artists of the Golden Age—these were simply and obviously unknown in the Catholic nations where the great wealth and patronage lay, aside from the constant and satisfactory demand at home in Holland which consumed the supply.

There were exceptions, and among the most notable is Rembrandt. The most powerful and gifted of all the Dutch, a failed and bankrupt prophet in his own land, Rembrandt's name was known in his middle period and at the height of his comtemporary fame throughout Europe, but in quite a special way—for let us remember that Rembrandt made many etchings of great and obvious quality and that these traveled easily. Don Antonio Ruffo, a prince in Sicily, had the means to commission and buy what he wanted and was well acquainted with art. Most of his collection was painted for him by the leading Italians of his day, and he was luckily ignorant enough of Rembrandt's late career difficulties to have him paint the now famous *Aristotle Contemplating the Bust of Homer.* Apparently Prince Ruffo did not like it nearly as much as earlier and less ambitious —more "Dutch"—Rembrandts he had commissioned. Nor could he have liked it much, for such subjects were to the baroque taste, handled better otherwise than in this now terribly expensive and terribly profound picture of an old man in odd, exotic costume sadly touching the bust of another old man.

Not until the end of the century would Cosimo III, Grand Duke of Tuscany, visit Holland and fall in love with paintings by Vermeer and William van de Velde, the great marine painter. Not until the 1740's would the British begin to systematically and intelligently drain Holland of some of its best masterpieces so that Cuyp and many others simply can't be seen except *out* of Holland. Not really until the 1670's did the greatest of Amsterdam dealers even *begin* to export anything but the best Italian masters bought and collected in Holland for sale, or those numerous Italianate Dutchmen, who are not the first Dutch painters we think of today and who painted Italian scenes with limpid southern skies in clear classical orders and harmonies.

The most famous Dutch artist in 1700 was a now forgotten and neglected figure, Adrian van der Werff, called in 1721 by the learned critic, Houbraken, the greatest of all Dutch painters. Van der Werff's small and beautifully finished figures would seem by classical Dutch standards—such as those of the artists of 1640 and also those of the Aldrich Collection almost perverse, over-precious, porcellainy and rococo flies in dark amber. He was perfect for a late baroque or rococo boudoir where a Ruisdael, a Rembrandt, or even that incredible masterpiece in this exhibition by Verhout would have looked like a bull in a china shop. But as Mme. de Pompadour failed and died, the French amateurs became able to like Rembrandt and Metsu, as well as the now widely popular Italianate Dutchmen such as Dujardin and Berghem, who now deeply in-

(Fig. 2)

fluenced French 18th Century landscape painting, almost a century after their own time. Even for the British of the 18th century the Dutch artists favored and collected had to be genial and Italian, and I can only count a minority of the paintings in the present exhibition which would have then made the grade.

These would have included the bosomy Bronchorst, *(Fig. 1)* for reasons apparent in any century, most of the landscapes (which the more romantic Englishmen would have loved), the Wouvcrman, which is an Italianate genre scene—and the landscape by Jan Wynants, which is exactly what the young Gainsborough loved, and through the freshness and immediacy of which he was to liberate his genius and that of British art. That gem of an early Rembrandt which you have the privilege of seeing here would have been respected anywhere in Europe, even in the 17th century, right on from about 1630 when it was done. In the 18th century it would have become a valuable and celebrated work—it was engraved in a prominent French collection at that time, and one may remember that not only did Sir Joshua Reynolds claim to base his own painting style upon Michelangelo and Rembrandt, but that such surprising artists as Tiepolo and Fragonard were fully aware of Rembrandt, venerated him, and even aped his manner, if not his profundity.

If Dutch painting was collected with avidity in Britain and France in the 18th century, the beginnings of its careful study and connoisseurship only began by virtue of the impending romanticism and within the brilliant eccentricities of random collectors who, however, only opened the door a crack to some of the most exciting virtues and artists. George III was thought cheated when a rather cheap Van Mieris turned out to be only by someone called Vermeer (now probably the most thrilling of the Queen's many Dutch pictures) and the paintings by the same great Vermeer which Catherine the Great had bought in Amsterdam and which were lost in a shipwreck on their way to Russia were apparently not much regretted at the time and were probably bought as satisfactory to Italianate taste in a century still so very Italianate in taste.

The heroics of the Napoleonic age weren't a good time for Dutch virtues, but I can quickly conclude my tale of collecting by noticing that the naturalness and severe real-

Anthony M. Clark—Director, The Minneapolis Institute of Arts.

(Fig. 3)

ism of the Bega, *(Fig. 2.)* the Brouwer, the several still lives in the Aldrich collection, the Jacobus Vrel, and the incredible Verhout could only have been appreciated universally with the coming of the 19th century and its scientific and social realism. How much the 19th century owes to pictures like this, how much we all owe! The Brouwer, a simple grimacing man, *(Fig. 3.)*, is a funny picture, but also a realistic physiological study that by empathy pulls our own muscles comically out of shape too, and makes us laugh. As all great comic art, it is factual and more than a caricature, it is a human and humane release. The Verhout portrait of an unpretentious brewer (see front cover) is as beautiful a piece of still life painting, and as original, daring, and elegant a work of art as anything I know. It is also, for all its intense simplicity and tiny format, as classical and potent as the finest Greek statues of the late archaic and early classical period. It is utterly clean and fresh, and as moving and great a piece of human creation, technique, and insight as possible to make. By 18th Century taste it would have seemed severe and even crude.

With the 19th century and our own day it became possible to see Dutch painting of the great period fully and well. That it is still possible to form, with modest means and sensible industry and shrewdness, such a collection as the Aldrich collection—in this day and age, could seem a hilarious comment on the modern art market, as well as an extraordinary evidence of a collector's talent. Indeed, it is both, but much more. As your Fifth Anniversary Fund seeks and achieves the excellent purposes of your Institute of Arts, consider and remember this collection. It does *not* take megalopolitan funds to gather and to share finest examples of man's best treasures. Works of art contain the meanings and virtues that are going to keep man alive and, if anything can, make man better. Your Fund permits you to see and to have this life-bread. Aldrich's example should show you that with energy, invention, and persistence, those natural and common qualitites of human existence, each of you can discover and achieve something important in collecting, in creating, or in simply subsisting, and all of you can achieve the purposes of the present campaign or, indeed, of any other social purpose you can think of.

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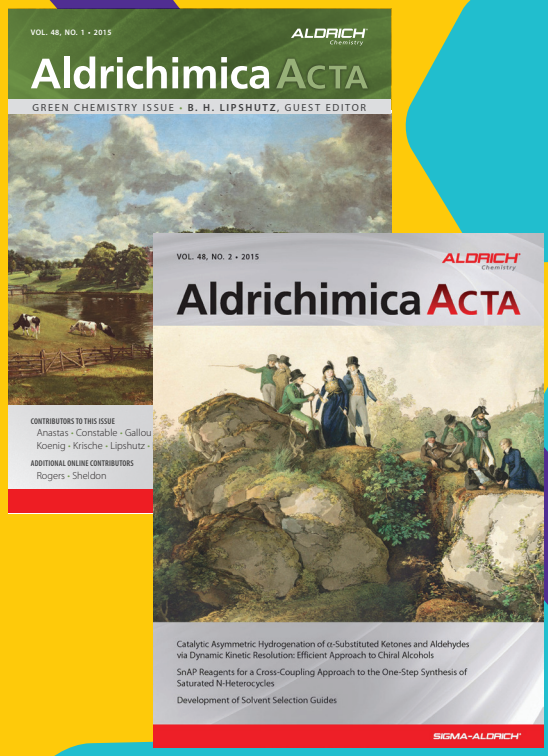

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