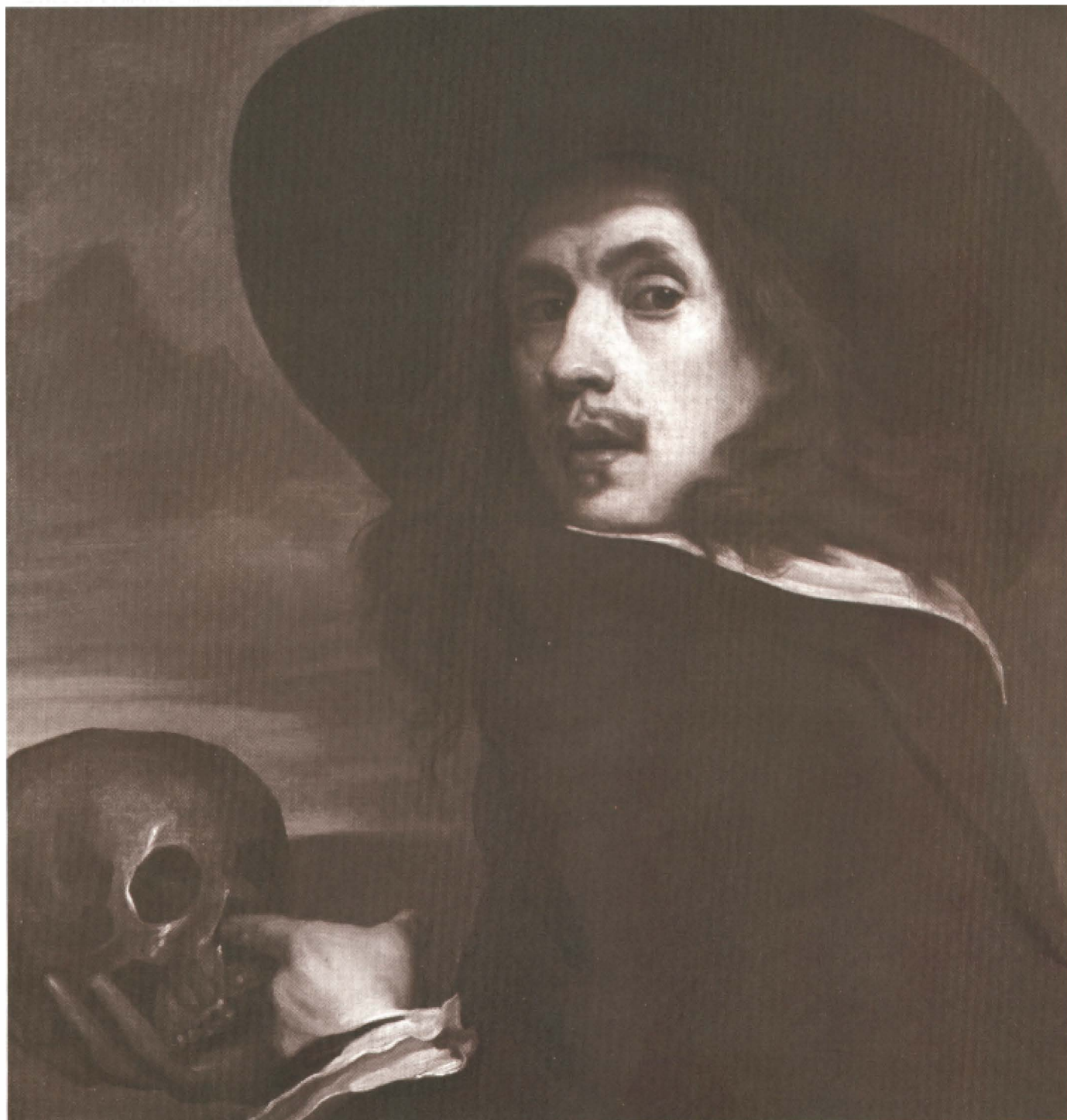


Aldrichimica acta

VOLUME 2, NUMBER 1, 1969



PUBLISHED BY THE ALDRICH CHEMICAL COMPANY, INC.

ABOUT THE COVER

One of the least understood and most interesting artists of the 17th century was Michael Sweerts whose self-portrait you see on our cover. Flemish by birth, Dutch and Roman by artistic education, Sweerts combined in his very personal style elements of Caravaggio and the Dutch Masters. In his late thirties he joined a religious mission to the Middle East, was asked to leave the mission in Persia in 1662 and died two years later in Goa, India. Before our chemist who collects old master paintings acquired this intense portrait, then unnamed, at a Munich gallery last summer, the skull had been overpainted by a shipping scene which was easily removed. The features of the artist and also the soft hands are similar to those of other Sweerts self-portraits, and this painting has now been accepted by art experts as one of Sweerts' self-portraits.

TABLE OF CONTENTS

The Evolution of Totally Synthetic, Strong Analgesics . . .	3
Computer Search of the Month	7
Chemicals of Special Interest	9
New Chemical Offerings	10
Computer Aids Search for R & D Chemicals	17

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Milwaukee, Wisconsin.

Editor, Kathleen D. Ryan

MEMO FROM THE LABORATORY

See page six for exciting new tool for the study of morphine tolerance and physical dependency.

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The Evolution of Totally Synthetic, Strong Analgesics

Everette L. May: Chief, Section on Medicinal Chemistry, National Institutes of Health, Bethesda, Maryland

The use of opium for the relief of pain and distress dates from antiquity. Until the invention of the hypodermic syringe by Christopher Wren (about 1850) opium was either smoked or eaten. This invention, the isolation of morphine from Opium by Sertürner (1803), and the synthesis and clinical use of diacetylmorphine (heroin) in the late 1890's presaged the modern age of potent pain-relieving agents with all its advantages and problems, medical and social.

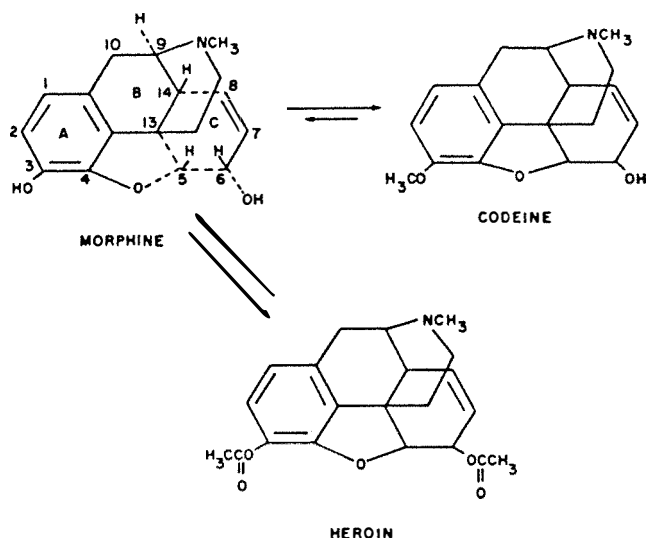


Fig. 1. Chemical structure of morphine, codeine, and heroin.

Thus, for well over a half century, especially since the chemical architecture of morphine became known and the interrelations of morphine, codeine and heroin (Fig. 1) were fairly well understood, scientists of various disciplines

have toiled diligently to develop substances with morphine-like, pain-relieving efficacy and negligible adverse effects particularly abuse liability. Early attempts consisted principally of modifications of morphine and codeine or of the toxic, medically useless thebaine which occurs in opium along with morphine and codeine and is closely related chemically. Of the hundreds of congeners made (some of which are shown in Fig. 2) none has attained more than limited medical use, usually in restricted clinical situations.

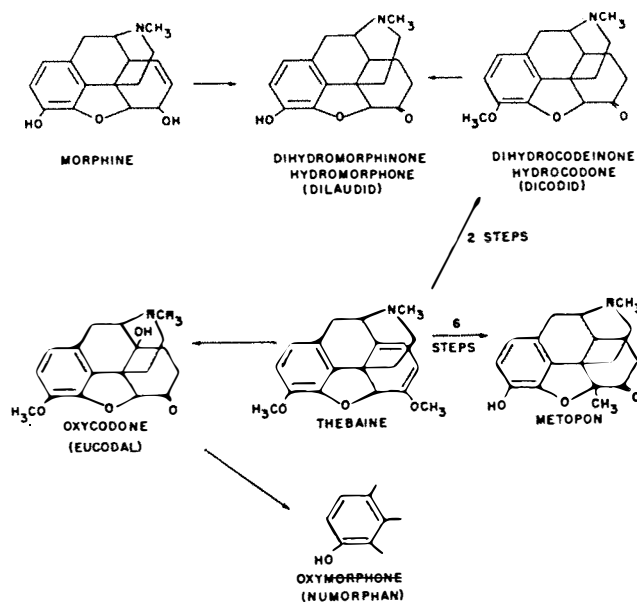


Fig. 2. Chemical structure of congeners of morphine.

And, with the possible exception of metopon (5-methyl-dihydromorphinone) prepared in the systematic studies of Small, Eddy, and Mosettig (1929-1939), any change in analgesic potency has been paralleled in general, by changes in deleterious effects including those of dependence liability, a term now preferred to addiction liability.

Equally discouraging were efforts directed toward the total synthesis of structures simulating various portions of morphine. In these efforts, morphine was considered as a phenanthrene, a dibenzofuran, an isoquinoline, a piperidine, etc. with phenanthrene the most frequently used fundamental structure again by the Small-Eddy-Mosettig group. However, the serendipitous discovery of pethidine (Demerol, meperidine) by two astute German investigators, Eisleb and Schaumann, a chemist and a pharmacologist, provided a breakthrough in 1939 which added a new dimension and direction to the search for totally synthetic analgesics. After it was found that pethidine, which was really modeled after cocaine as a spasmolytic agent, was a morphine-like analgesic agent, albeit of lesser potency than morphine, these investigators discerned that pethidine represented a substantial fragment of morphine as shown in Fig. 3.

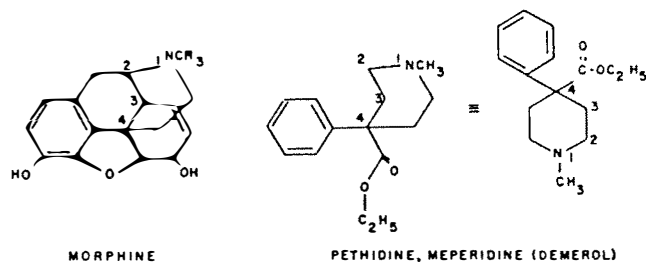


Fig. 3. Chemical structure of pethidine.

Pethidine has become a popular and valuable analgesic but possesses the same general drawbacks as morphine and a shorter duration of action. Perhaps more importantly, its advent stimulated the synthesis of hundreds of analogs, the more prominent of which are shown in Fig. 4, and more divergent structures such as methadone which was developed in World War II, also in Germany (Bockmühl and Ehrhart). The pharmacologic profile of methadone, whose structural resemblance to morphine is depicted in Fig. 5, is similar to that of morphine, although it is much more effective orally and longer acting. It is presently under

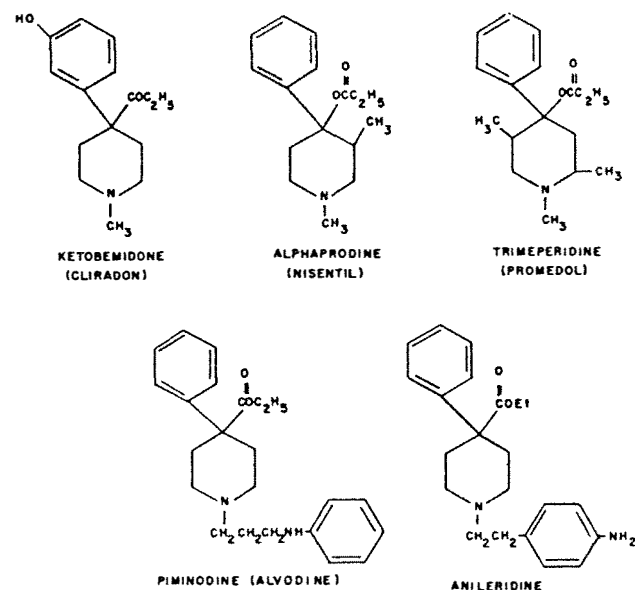


Fig. 4. Chemical structure of analgesic compounds related to pethidine.

investigation (Dole, Nyswander) in maintenance and rehabilitation therapy for heroin and morphine addicts, apparently with marked success. *d*-Propoxyphene (Darvon), discovered by Pohland, *et al.* and dextromoramide (Janssen) are practical developments arising from methadone (see Fig. 6).

a tertiary amino group two carbons removed from the quaternary carbon. Note, however, that the tertiary nitrogen of methadone is aliphatic or open in contrast to the heterocyclic (ring) nitrogen of morphine and pethidine.

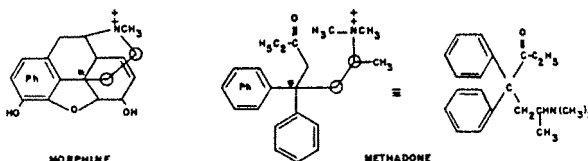


Fig. 5. Structure of methadone.

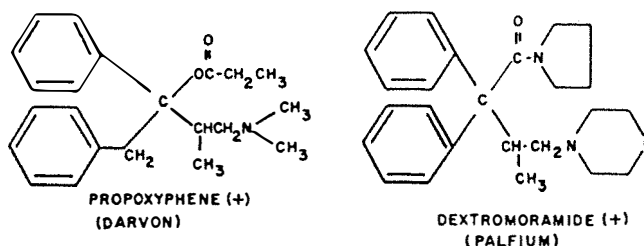
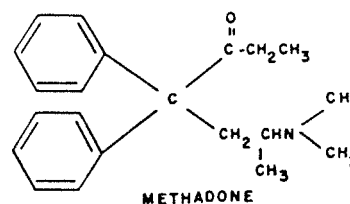
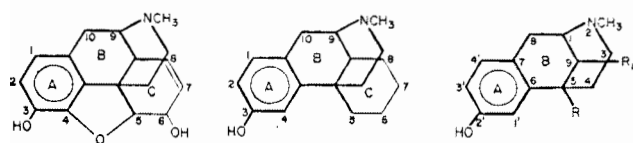


Fig. 6. Structure of *d*-propoxyphene and dextromoramide.

Almost simultaneously with the emergence of methadone came another important advance in synthesis, the morphinans which resulted indirectly from one of the early attempts at the total synthesis of morphine, again by a German chemist, Rudolph Grewe. The best-known analgesic of this series (-)-3-hydroxy-N-methylmorphinan (levorphanol Fig. 7), contains the complete carbon-nitrogen framework of morphine but lacks several of morphine's peripheral functional groups. It is, nevertheless, four times as potent as morphine on a dosage basis with good oral effectiveness. A tangential development and fringe benefit of the morphinan research was the discovery of an effective, non-narcotic antitussive, (+)-3-methoxy-N-methylmorphinan (dextromethorphan), the methyl ether of the enantiomorph of levorphanol. Levorphanol and dextromethorphan are due to Schneider, *et al.*

Still further alteration and simplification of the molecule (deletion of part of the terminal hydroaromatic ring C, Fig. 8) has provided 6,7-benzomorphans (National Institutes of Health) with the intact iminoethano system and other structural features of morphine believed essential for strong, central analgesic action. These compounds as racemates have shown a consistent separation of morphine-like analgesia (referred to the mouse and rat) and physical

dependence properties (tests in monkeys). Never before has any substantial divorce of these advantages and disadvantages been demonstrated for a class of compounds even in animal species. This separation is not entirely species related but is shown to apply partially to man in the few compounds so tested. One N-substituted derivative, (\pm)-5, 9-dimethyl-2-hydroxy-2-phenethyl-6, 7-benzomorphan (Fig. 8) has been marketed in the United States as Prinadol and in England as Narphen. It has a broad pain-relief spectrum, 3-5 times the milligram potency of morphine, oral effectiveness and less abuse liability than morphine.



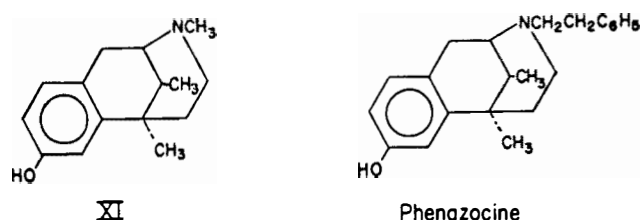
I Morphine (-)

II Levorphanol (-)

III 6,7-Benzomorphan

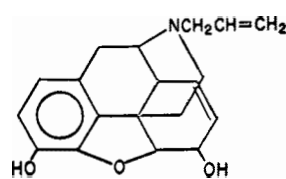
Fig. 7

Based on these findings and on the discovery of strong analgesic activity for the non-dependence producing, narcotic antagonist, nalorphine, Archer Harris, *et al.* have synthesized a series of antagonists of varying degrees of

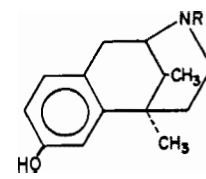


XI

Phenazocine
(Prinadol, Narphen)



Nalorphine

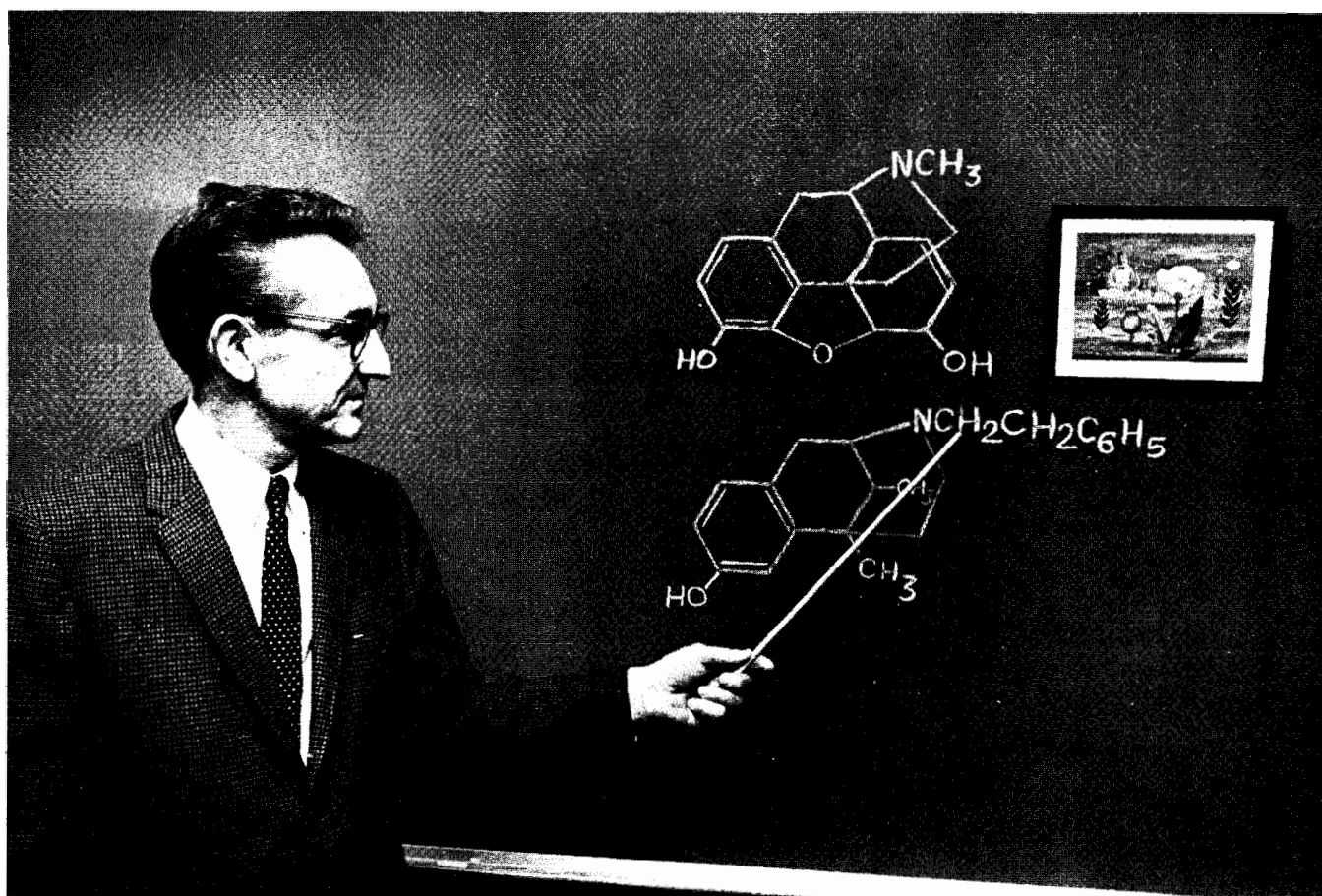


R = CH₂Δ-Cyclazocine

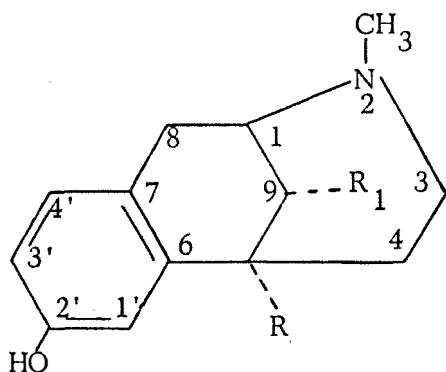
R = CH₂CH=CMe₂-Pentazocine

Fig. 8

potency by substituting other hydrophobic groups for the methyl of 2'-hydroxy-2,5, 9-trimethyl-6, 7-benzomorphan (Fig. 8). The 2-(N)-cyclopropylmethyl analog (cyclazocine) is not only a strong narcotic antagonist but is also



Dr. May discussing structural differences and similarities of morphine and phenazocine.



- Ia $R = R_1 = \text{Me}$
- b $R = R_1 = \text{Et}$
- c $R = \text{Me}, R_1 = \text{H}$
- d $R = \text{Et}, R_1 = \text{H}$
- e $R = \text{Pr}, R_1 = \text{Me}$

Fig. 9

a powerful, orally effective analgesic in man without substantial abuse liability. It appears to be useful (Freedman) as a deterrent and rehabilitation agent in heroin and

For a detailed treatment of Morphine-like and peripherally acting analgesics, see "Analgetics", G. deStevens, Ed., Academic Press, Inc., New York, N. Y. 1965.

morphine abuse. Pentazocine, the dimethylallyl congener (Fig. 8) is marketed as a non-narcotic analgesic, Talwin, 20-40 mg. being as efficacious, it is claimed, as 10 mg. of morphine in most types of pain.

Finally, optical resolution of several of the racemates of the benzomorphan group containing methyl on the nitrogen (Fig. 9) has resulted in further separation of morphine-like effects. Thus, the *levo*-isomers (in some instances twice as potent as morphine) contain almost all the activity elicited by the racemates, yet have no capacity to substitute for morphine in an established physical dependence in rhesus monkeys. In fact, these *levo*-antipodes will actually precipitate or exacerbate abstinence signs, being nalorphine-like in this respect. Apparently, they will also antagonize some of the (undesired) effects of their weakly analgetically effective *dextro*-counterparts which, surprisingly, have from low to high physical dependence capacity in monkeys; in all cases, the racemates from which these *levo*- and *dextro*-isomers are derived have very low or no physical dependence capacity. It is already known that the *levo*-isomers are excellent pain-relieving agents in man, so that if the results obtained in monkeys are also quantitatively transferred to man, the near-ideal strong analgesic may be at hand.

In any event, with the plethora of efficacious, totally synthetic analgesics and antitussives now extant, several of which are much less likely to be abused than morphine and heroin, mankind would not be handicapped without opium. It is possible even probable that if opium, the only ready source of morphine, codeine and heroin, were to be extinguished, the problem of drug dependence of the morphine type (narcotic addiction) would be greatly alleviated.

Featured Biochemical of the Month

p-CHLOROPHENYLALANINE

A Powerful Biological Tool in the Study of the Physiological Role of Serotonin and its Relationship to Morphine Tolerance and Physical Dependence

p-Chlorophenylalanine, our product number 13,071-0, is a potent inhibitor of the 5-hydroxylation of tryptophan which is the rate-limiting step in the synthesis of serotonin. This has been demonstrated in both animals¹ and man.^{2, 3, 4}

The most intriguing findings are those by Way et al.⁵ who have shown in mice that the prior administration of p-chlorophenylalanine will markedly decrease tolerance

and physical dependence to morphine which would implicate either 5-hydroxytryptophan or serotonin in the production of these effects.

1. B. K. Koe and A. Weissman, *J. Pharmac. Exp. Ther.*, **154**, 499 (1966).
2. V. Y. Cremata and B. K. Koe, *Clin. Pharmacol. Therap.*, **7**, 769 (1966).
3. W. Studnitz, J. Waldenström and P. Mikulowski, *Lancet*, **II**, 564 (1967).
4. K. Engelman, W. Lovenberg and A. Sjoerdsma, *New Engl. J. Med.*, **277**, 1103 (1967).
5. E. L. Way, H. H. Loh and F. Shen, *Science*, **162**, 1290 (1968).

Computer Aids Search for R&D Chemicals

Aldrich Chemical plans to gather up to 50,000 rare chemicals from all over the world into a catalog system through which individual chemicals can be retrieved by computer

Where in the world can a research chemist purchase a compound that has certain specified structural characteristics? Aldrich Chemical may have an answer to that in a year or so. If it carries through on its current plans, the Milwaukee company will be extending its present computer chemical search system to a worldwide chemical locating system.

Through the locating system an organic research chemist would be able to tune in on some 40,000 to 50,000 research and development compounds. Even now, Aldrich's system holds some 15,000 organic chemicals—more than 9000 from its own catalog as well as the rare chemicals from its Alfred Bader chemicals division catalog. A chemist wanting to know what chemicals meeting certain structural requirements exist in the catalogs can request a search. He receives a computer printout listing all the chemicals meeting the requirements—cyclic 7-, 8-, or 9-carbon amines, for example. The service is provided to the chemist free of charge.

Aldrich has a strong base to build on for a worldwide locating system. As a supplier of organic research chemicals—both common and rare—the company has learned of or had to search out sources. Aldrich itself produces about 1500 of the chemicals it markets. Some 3000 to 4000 are made specifically for it. The remainder are purchased.

William Buth, Vice President and Director of Operations at Aldrich, explains that in building up its sources, Aldrich now owns wholly or in part a number of foreign production and distributing companies that make or get chemicals for it. These companies in turn have sought out hundreds of other sources. All of these would be gathered together and stored in the computer for the locating system.

Several problems concerning the system have yet to be resolved, so the final decision to go ahead hasn't yet been made. But, Mr. Buth says, Aldrich is seriously moving in this direction.

One problem is a catalog. The way the current system works, a chemist requests a list of compounds available that have certain structural configurations. The computer printout then lists the name and catalog numbers for the Aldrich chemicals, just the numbers for the Bader rare chemicals. The chemist can then look in the catalogs for the structural drawings and decide which, if any, he might want to order.

The problem arises in that a catalog listing names and structural formulas for 40,000 to 50,000 chemicals would likely be prohibitively expensive—especially if the locating service is provided free, as is the present service. Consequently, Aldrich is considering a locating service without a catalog, but isn't sure that it would be very successful.

Alternatively, it might be possible to include structures on the computer printout.

It was a catalog problem, in fact, that led Aldrich to set up its present system. To keep printing and distribution costs for its catalog within reasonable bounds, the company must periodically remove chemicals that sell poorly to make room for newer additions. The removed chemicals, however, are generally rare and unusual molecules that the company is reluctant to throw out. So it gathers them together and sells them through the Alfred Bader chemical division.

Since demand is low—each chemical might on the average generate one sale every couple of years—full cataloging was too costly. Thus the company produced a catalog including only structural formulas cross-referenced with empirical formulas. Correct chemical names were too expensive to ascertain and use. A rapid indexing system was required, however, so the computer search system was devised and extended to all the company's chemical products.

Coding all the chemicals for a worldwide locating system will probably take about a year. Coding for its present system has been mostly a spare-time activity for Aldrich. The coding system used is based on structural fragments and, as such, is not unlike the systems used by a number of chemical companies. Before taking this approach, Mr. Buth says, several systems were studied for possible use, including the *Chemical Abstracts* system. Most of them turned out to be too intricate, too costly, and too specific for Aldrich's purposes.

In the structural fragment approach, a chemical is coded by its geometry and not by its chemical characteristics. Phenol, for example, is a hydroxyl group and a six-membered carbon ring. About 240 fragments are used by the system to define compounds.

Single rings are coded separately from fused-ring systems. Single rings can be retrieved even if they are part of a larger fused-ring system. Hetero atoms can be specified but not position. Also, fragments, rings, and atoms can be excluded from the search.

The result is a system designed to retrieve pertinent compounds from an almost random selection of organic chemicals. It's a noisy type of retrieval, Mr. Buth points out, in that a number of undesired retrievals will show up. This can be held down, however, by properly combining specifications and exclusions.

Mr. Buth says that some extraneous retrieval is actually desirable. Most users, he points out, are looking for families of chemicals, not single compounds. A certain level of questionable retrievals—chemicals that are like but not obviously identical to the requested information—can provide the chemist with possible new ideas or materials.

Aldrich is satisfied that the service has been successful so far, even if it hasn't yet been able to correlate its use with sales. The company is now processing 60 to 70 requests per week and the number is growing. Cost is low. The company has the computer for its own bookkeeping anyway, and the typical request takes but one and a half minutes of computer time.

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Available Literature

Thallium ethoxide. Reacts with β -dicarbonyl compounds, which can be acylated, aroylated and tosylated in high yields. Product No. 14,984-5.

EEDQ. Reagent for preparing peptides and amides. Product No. 14,983-7.

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

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ABOUT THE COVER

This beautiful view of St. Vitus' cathedral in Prague was painted by R.v. Alt in 1850. Despite the fact that it is not a Dutch 17th century painting, our chemist-collector considers it the most beautiful architectural painting in his collection. For a discussion of Prague today, see page 15.

TABLE OF CONTENTS

The Wittig Reaction	3
Computer Search of the Month	7
Chemicals of Special Interest	9
New Chemical Offerings	10
Prague Revisited	15

MEMO FROM THE LABORATORY

See page 18 for versatile new tool in amide and peptide syntheses.

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The Wittig Reaction

Harvey B. Hopps and John H. Biel, Research Division, Aldrich Chemical Company, Inc.

SUMMARY

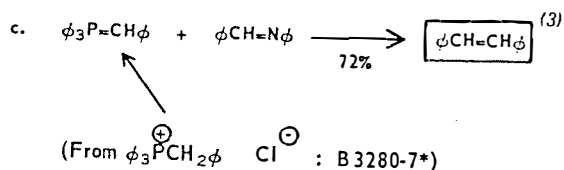
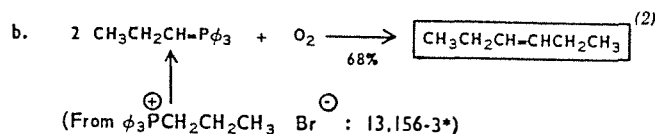
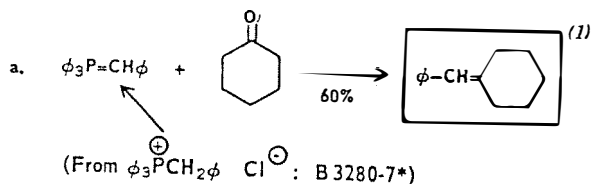
The Wittig reaction represents one of the most versatile and practical developments in synthetic organic chemistry which have appeared during the past fifteen years. This article is designed to publicize in a survey form the synthetic scope of this reaction which lends itself so readily to the facile preparation of all types of olefins; aldehydes; ketones; acids; nitriles; α , β -unsaturated aldehydes, ketones and acids; acetylenic acids and ketones; keto acids; cyclopropanes; cyclopropanecarboxylic acids and nitriles; alicyclic and certain heterocyclic derivatives.

It has always been the philosophy of Aldrich to be in the forefront of new synthetic organic developments and make available in bulk those reagents that would be of greatest benefit to the organic chemist in his quest for the building of novel structures from relatively inexpensive starting materials.

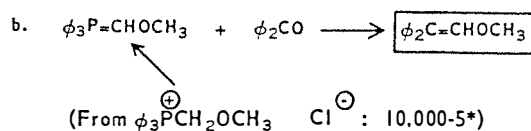
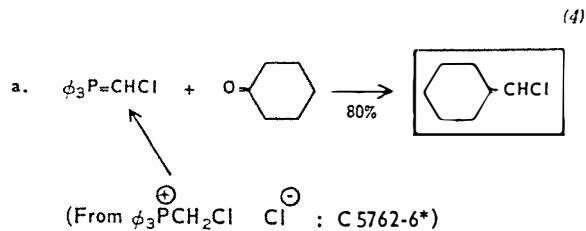
The Wittig reagents represent such a class of compounds and we have outlined below the principal categories of products which may be obtained quite readily through the use of these valuable reagents.

(1) The Preparation of Olefins^(1, 2, 3)

Alkylidene and aralkylidene triphenylphosphines may be converted to olefins in high yields by allowing them to react with the appropriate carbonyl compounds, oxygen or Schiff's bases, viz.:



(2) Halogen and Alkoxy Containing Olefins^(4, 5)

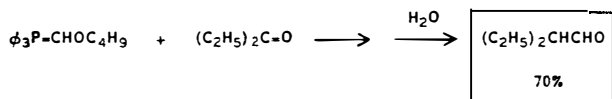


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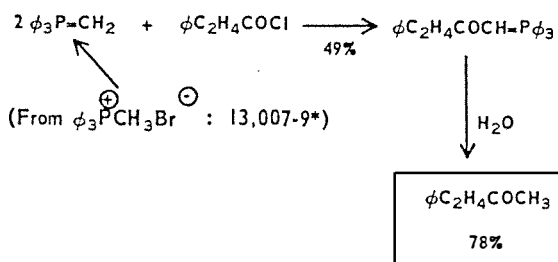
(3) *The Preparation of Aldehydes*⁽⁶⁾

The above alkoxymethylidene triphenylphosphines can be utilized also in the production of all types of aldehydes from the required ketones as illustrated below:

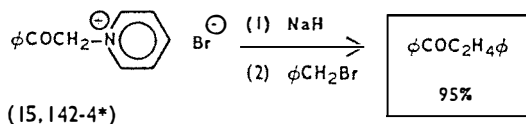


(4) *The Preparation of Ketones*⁽⁷⁾

a. Acid chlorides interact readily with phosphonium ylids to yield the desired ketones via a two-step synthesis:

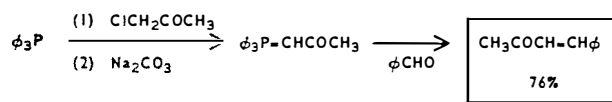


b. An additional way of forming ketones via the ylid reaction is to allow N-pyridinium phenacylid to react with active halides to afford the desired ketones in excellent yields.^(7a)



(5) *α, β -Unsaturated Ketones*⁽⁸⁾

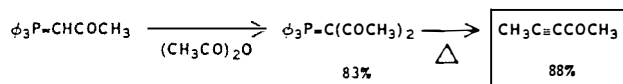
Ylid formation of triphenylphosphine with chloroacetone followed by reaction with a carbonyl reagent will afford α, β -unsaturated ketones in good yield:



(T 8440-9*)

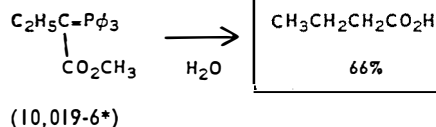
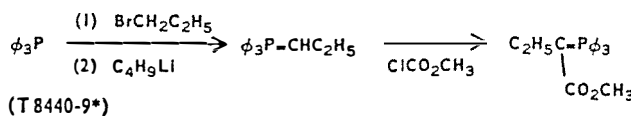
(6) *Acetylenic Ketones*⁽⁹⁾

The above ylid may also be reacted with acetic anhydride to form acetylenic ketones in high yield which would be difficultly obtainable otherwise:



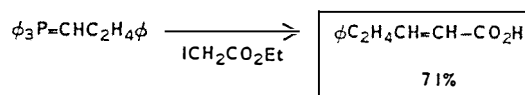
(7) *The Preparation of Acids*⁽¹⁰⁾

Acids of varying chain lengths may be prepared from triphenylphosphine, an alkyl halide, and interaction of the resulting ylid with ethyl chloroformate as illustrated below:



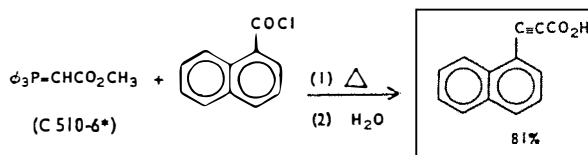
(8) *α, β -Unsaturated Acids*⁽¹¹⁾

An alkylidene or aralkylidene triphenylphosphine when allowed to interact with an α -halo acid ester will produce α, β -unsaturated acids in good yield:



(9) *Acetylenic Acids*⁽¹²⁾

Carboxymethylidene triphenylphosphine methyl ester may be reacted with acid chlorides to form α, β -acetylenic acids:

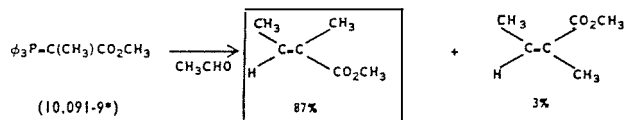


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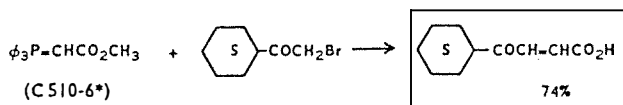
(10) *Formation of α, β -Unsaturated Esters from Aldehydes⁽¹⁵⁾*

A carboxyalkylidene triphenylphosphine methyl ester will react with aldehydes affording high yields of the *cis*- α, β -unsaturated acids:



(11) *α, β -Unsaturated Keto Acid Esters⁽¹⁴⁾*

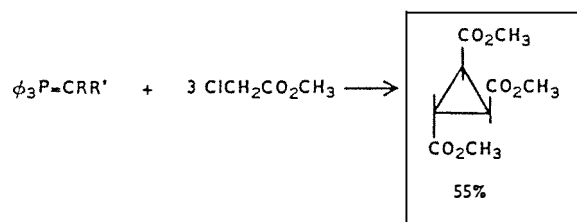
Carbomethoxymethylidene triphenylphosphine and an α -halo ketone will react to give α, β -unsaturated keto acid esters according to the following scheme:



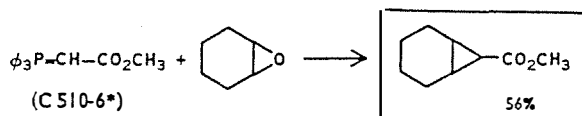
ALICYCLIC SYSTEMS

Alicyclic compounds may be obtained *via* the Wittig reaction as shown in examples 12-16:

(12) *Cyclopropanetricarboxylic Acid Esters⁽¹⁵⁾*

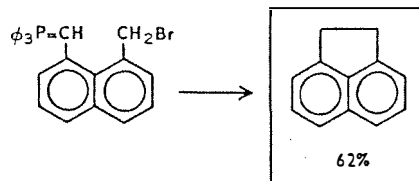


(13) *Fused Cyclopropane Ring Systems⁽¹⁶⁾*



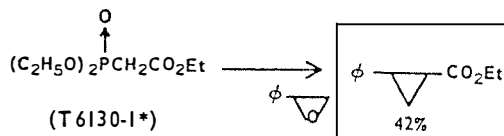
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(14) *Fused Aromatic Alicyclic Ring Systems⁽¹⁷⁾*

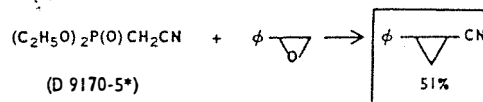


(15) *Cyclopropanecarboxylic Acid Esters⁽¹⁸⁾*

The reaction of triethyl phosphonoacetates with ethylene oxides is another means of obtaining cyclopropanecarboxylic acid by a one-step synthesis:



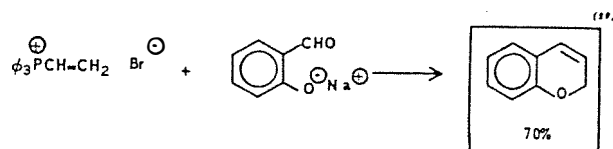
(16) *Cyclopropane Nitriles⁽¹⁹⁾*



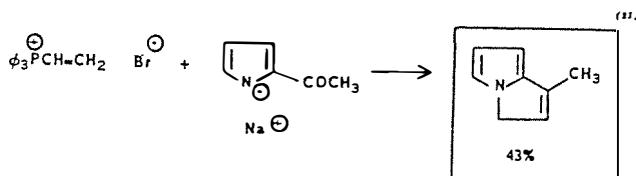
HETEROCYCLIC SYSTEMS

Certain heterocyclic ring systems may be produced *via* the Wittig reaction as illustrated by examples 17-19:

(17)

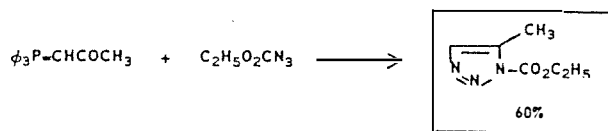


(18)



*Aldrich catalog numbers

(19) *Triazoles*⁽²²⁾



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- (5) Vinyl Ethers
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- (6) Aldehydes
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- (7) Ketones
H. J. Bestmann and B. Arnason, *Chem. Ber.*, 95, 1513 (1962).
- (7a) C. A. Henrick, E. Ritchie, and W. C. Taylor, *Australian Journal of Chemistry*, 20, 2441 (1967).
- (8) α, β -Unsaturated Ketones
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- (9) Acetylenic Ketones
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- (10) Acids
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- (11) α, β -Unsaturated Acids
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CONCLUSIONS

As stated in the introduction, this article is meant to highlight the plethora of synthetic possibilities afforded by the Wittig reaction. The reader is also referred to several important review articles listed in the bibliography which have appeared during the last five years, as well as the "Search of the Month" section in this issue which gives a computer print-out of the Wittig reagents available from Aldrich (p. 7).

- (12) Acetylenic Acids
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- (13) α -Substituted- α, β -Unsaturated Esters
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- (15) Cyclopropanes
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b. D. B. Denney, J. J. Vill and M. J. Boskin, *J. Amer. Chem. Soc.*, 84, 3944 (1962).
- (16) Cyclic Compounds
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- (17) Cyclopropanecarboxylic Acids, Esters and Nitriles
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- (20) Triazoles
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- ii. S. Trippett, *Quarterly Reviews*, 17, 406 (1963).
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Prague Revisited

Alfred R. Bader

Ever since I was a boy, Prague has been one of my favorite cities. As a boy I had spent several summers with friends of the family living in a small town in Moravia, and the highlight of each summer had been a brief trip to Prague—das goldene Prag—my mother had called it. Between the wars, Prague was a most prosperous city; stable, busy, beautiful to look at, the most western of all Slavic cities. But what intrigued me the most was not the beautiful view of Prague with its 100 church steeples^(fig. 1), or its lovely baroque architecture^(fig. 2, 3), but the old town with its dozens of spooky, narrow streets and particularly the Jews' ghetto nestling into one corner, at the bend of the river Moldau. Here was the unbelievable cemetery, dating to the 15th Century, so crowded that it contained twelve layers of graves, the top—on which you walked—many feet above street level—with thousands of gravestones side by side. This had been the only bit of green in the entire ghetto, and each summer I had stood there for a little while, watching the many visitors—many of them pious Jews saying prayers at this or that grave of a famous rabbi—and I had wondered what life in the ghetto had really been like. I had also been scared by the legend of the Golem, the robot said to have been built by the most famous of all the rabbis of Prague, Rabbi Judah Löw, at the end of the 16th Century. The remains of this Golem were believed still to remain in the attic

of the oldest of the synagogues, and the whole atmosphere of the ghetto tended to lend credence to the legend.

For reasons that might seem more plausible in an Alec Guinness movie, much of the ghetto survived the Nazi occupation, even though few of Prague's Jews did. There is now in the ghetto one large hall, empty but for the names of thousands of Czech Jews that were killed, but someone persuaded Hitler that history would be well served if a Jewish museum were established in the Prague ghetto, to tell the generations to come what Jews had been like—long after the last one had disappeared from the earth. And so thousands of Jewish ritual objects and truckloads of Hebrew books were sent to Prague to fill this museum, and now the Prague Jewish Museum is probably the most interesting Jewish Museum in the world—and also the emptiest of people. In the two hours my wife and I spent in the cemetery and the adjoining museum and synagogues, we saw no one but the old care-takers.

When I had first returned to Prague, after the last war in 1949, I had also been scared, but for reasons quite different from the childhood fears of the Golem. The communist coup had taken place just a year before, and it was obvious to me that the few old friends who were



Fig. 1. Beautiful church steeples of Prague

left in Prague were afraid to talk to me. There was a great deal of blatant communist propaganda, closer in type to Nazi propaganda, than the spirit of Prague I had known. Since 1949 I had been back to Prague only very occasionally, and last December was my first visit after the Russian occupation. Prague now, as on each of the previous visits since the war, seemed very drab—many lines of people shopping for food and other necessities; people uniformly colorlessly dressed, and yet the people's spirit seemed quite different. There was obviously pride in the fact that no traitors whatever could be found by the Russians to collaborate with them, something that did

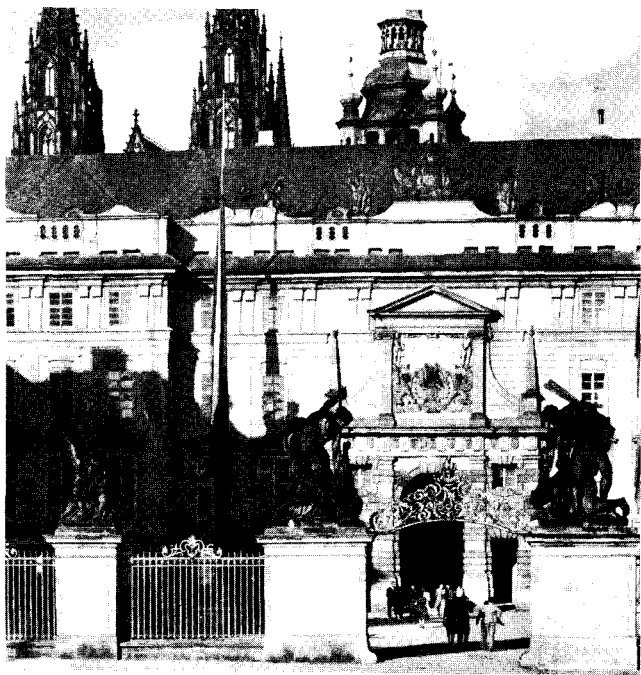


Fig. 2. Prague Court of Honor

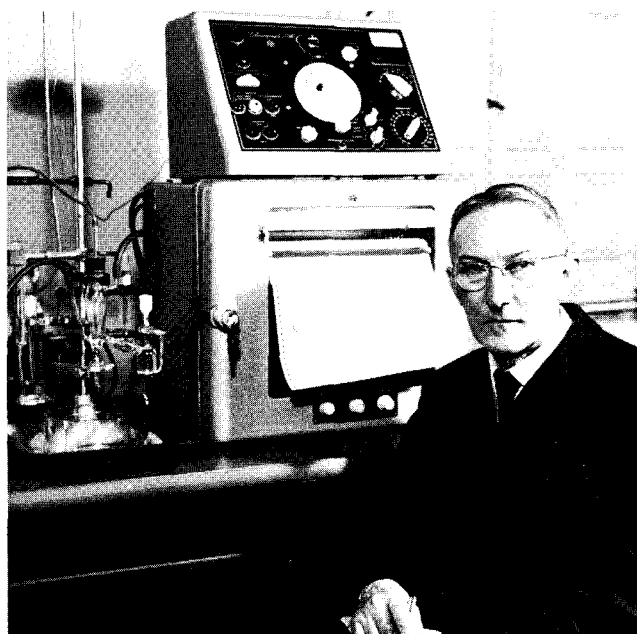


Fig. 4. Prof. J. Heyrovsky, Nobel prize winner

not occur even during the Nazi occupation when a great many Czech Quislings existed. Time and again, someone pointed out to me in one way or another that here was a historic first: Never before in recorded history has an entire people been absolutely unanimous in resisting—albeit passively—an invader. During my days in Prague, I saw only one lorry-full of Russian soldiers and a great many signs all over the city exhorting Czech leaders to be strong. Most surprising, there were also quite a few pictures of the George Washington of Czechoslovakia, Thomas G. Masaryk, who for many years had been labeled just another decadent, capitalist politician by the communists.



Fig. 3. Lovely baroque architecture of The Spanish Hall

Naturally, the main purpose of my trip to Prague was not to reminisce, but to discuss chemistry and chemical products with Czech chemists and with officials of the only organization in Czechoslovakia that acts both as the buying and selling agent of chemicals for all Czech industry and research, a company called "Chemapol." What strikes you most forcefully in your discussions with Czech chemists is firstly, their great and genuine desire to be in commercial and scientific contact with you, and secondly, the great difficulties which a communist society imposes on commerce, production and research.

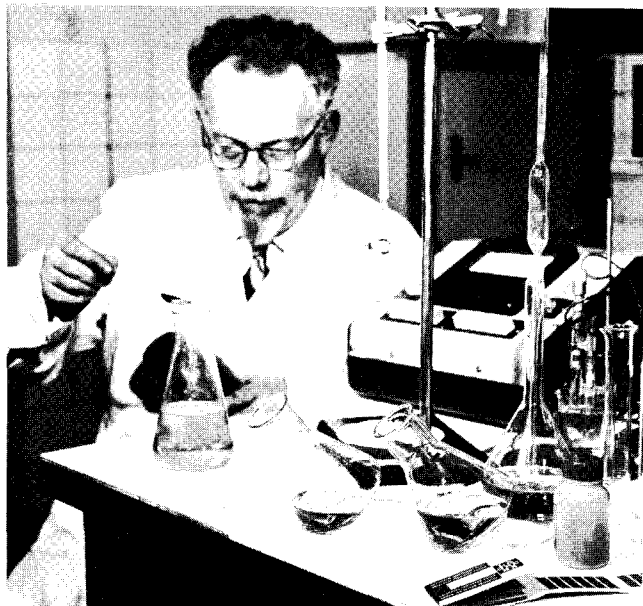


Fig. 5. Dr. Rudolf Pribil

Everything is completely organized and planned, and when talking about scheduled production and deliveries of even quite small amounts of new products, this can often be planned only for this or that quarter of the next year because the starting materials have to be obtained, and everything takes time. Communication is relatively simple; while my Czech is almost nonexistent, most

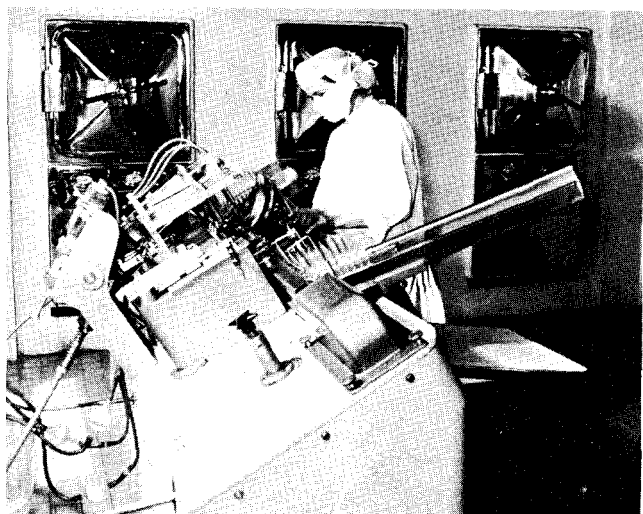


Fig. 6. Packaging of Pharmaceuticals



Fig. 7. Production of insulin

chemists over 40 speak German well, and most younger men speak English, often quite fluently.

Czech chemistry has considerable tradition, and is particularly proud of its Nobel prize winner, Professor J. Heyrovsky^(fig. 4), the father of polarography, and men such as Dr. R. Pribil^(fig. 5) who have done a great deal of research in analytical chemistry. Naturally the Czechs have developed many new analytical reagents, and are also doing a good deal of research in inorganic chemistry, particularly in the chemistry of uranium compounds and in organometallic chemistry. Thus, for instance, chemists at The Institute for Inorganic Syntheses have developed a most interesting reducing agent, sodium dihydro-bis-(2-methoxyethoxy)-aluminate—soon to be marketed by Aldrich—which acts somewhat like lithium aluminum hydride—but has the added advantages that it is soluble in many organic solvents, is quite stable to air-oxidation, reacts calmly with water and does not ignite spontaneously. Aldehydes and ketones, acids and esters are reduced to alcohols, and oximes and nitriles to amines, in yields generally somewhat higher than with lithium aluminum hydride.

Scientists at The Academy of Sciences are doing a good deal of medicinal chemistry, particularly in cancer chemotherapy with compounds such as 6-azauridine, and the production of pharmaceutical intermediates and standard products such as insulin^(fig. 6, 7) is well organized.

During my previous visits to Prague, it never happened that I was left alone with just one chemist or one Chemapol businessman—and I am sure that this was no accident. Now several talked to me alone, and much in the same vein—expressing the hope that there would return the spirit of the "Prager Frühling", the spring of Prague—a euphemism for what the spirit in Prague had been last spring, before the Russian invasion. It was a feeling I could easily share.

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