ELEVENTH NATIONAL ORGANIC

CHEMISTRY SYMPOSIUM

of the

AMERICAN CHEMICAL SOCIETY

★

Headquarters and Meetings — The Memorial Union of the
University of Wisconsin, Madison, Wisconsin.

Sunday, June 19 — Registration. The Memorial Union,
7:00 p.m. to 10:00 p.m.

Monday, June 20 — Registration. The Memorial Union,
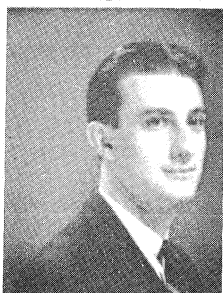8:00 a.m. to 8:00 p.m.

Tuesday, June 21 — Registration. The Memorial Union,
8:30 a.m. to 8:00 p.m.

Wednesday, June 22 — Registration. The Memorial Union,
9:00 a.m. to 12:00 noon.
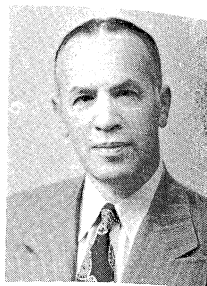
Homer Adkins

James Cason
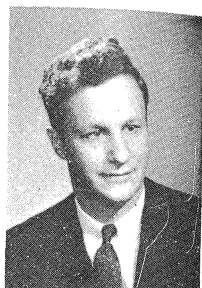
Lyman C. Craig

Karl Folkers
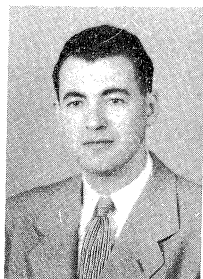
T. A. Geissman

M. S. Kharasch

Frank R. Mayo

Ralph L. Shriner

F. H. Westheimer

S. Winstein

M. L. Wolfrom

R. B. Woodward

Program

Monday Morning

9:00 A.M. Welcome. *Edwin B. Fred,* University of Wisconsin.

Response. *William G. Young,* University of California.

9:30 A.M. 1. *Ralph L. Shriner.* Heterocyclic Carbonium Salts.

10:30 A.M. 2. *F. H. Westheimer.* The Mechanism of the Mercuration of Benzene.

11:30 A.M. Discussion of papers 1 and 2.

Paper 1—Theatre.

Paper 2—Play Circle.

Monday Afternoon

1:30 P.M. 3. *M. L. Wolfrom.* Configurational Relationships and Configurational Standards.

2:30 P.M. Discussion of paper 3. Play Circle.

3:00 P.M. 4. *Homer Adkins.* Catalysis of Hydroformylation and Other Reactions.

4:00 P.M. Discussion of paper 4. Play Circle.

4:30 P.M. 5. *M. S. Kharasch.* Recent Advances in the Chemistry of Free Radicals.

5:30 P.M. Discussion of paper 5. Play Circle.

Monday Evening

8:30 P.M. Rathskeller Party. The Memorial Union.

Tuesday Morning

9:00 A.M. 6. *James Cason.* Branched-Chain Fatty Acids.

10:00 A.M. Discussion of paper 6. Play Circle.

10:30 A.M. 7. *Karl Folkers.* Some Aspects of Streptomycin Research.

11:30 A.M. Discussion of paper 7. Play Circle.

Tuesday Afternoon

1:30 P.M.	8. *S. Winstein.* Neighboring Group Participation in Some Chemical Reactions.
2:30 P.M.	Discussion of paper 8. Play Circle.
3:00 P.M.	9. *R. B. Woodward.* The Structure of Strychnine.
4:00 P.M.	Discussion of paper 9. Play Circle.
4:30 P.M.	10. *Lyman C. Craig.* Extraction.
5:30 P.M.	Discussion of paper 10. Play Circle.

Tuesday Evening

8:00 P.M.   Concert. Pro Arte Quartet. Theater.

Wednesday Morning

9:00 A.M.	11. *T. A. Geissman.* Metal Complexes.
10:00 A.M.	Discussion of paper 11. Play Circle.
10:30 A.M.	12. *Frank R. Mayo.* Polymerization and Free Radicals.
11:30 A.M.	Discussion of paper 12. Play Circle.

Adjournment

Madison Committees

★

The University of Wisconsin is acting as host for the organic chemists.

General Arrangements.................................. { Homer Adkins
{ S. M. McElvain

Registration.. A. L. Wilds

Rooms and Reservations.................................... B. F. Aycock, Jr.

Restaurant Facilities.. W. S. Johnson

Scientific and Social Meetings................................. M. W. Klein

Division of Organic Chemistry

The plans and program of the Eleventh National Organic Chemistry Symposium have been developed by the Executive Committees of the Division of Organic Chemistry who have served during the past two years.

	1947-48	1948-49
Chairman	Paul D. Bartlett	William G. Young
Secretary	Ralph W. Bost	Ralph W. Bost
	Arthur C. Cope	Paul D. Bartlett
	Ralph L. Shriner	Karl Folkers
	William G. Young	Harold R. Snyder

An Invitation to Organic Chemists who are not members of the Division of Organic Chemistry

The Executive Committee of the Division of Organic Chemistry extends to you a cordial invitation to become a regular member of the division.

Each of the divisions of the American Chemical Society serves a field of specialization and the Organic Division endeavors to serve organic chemists by furthering organic chemistry. To that end, it wishes to have associated with it as many organic chemists as possible.

The requirements for divisional membership are: (1) membership in the American Chemical Society, (2) active interest in organic chemistry, and (3) payment of annual dues of $1.50 These dues are used to pay the expenses involved in the activities of the division which are:

1. Mailing of notices and forms for the presentation of papers at the Spring and Fall Meetings of the A.C.S.

2. Lithoprinting and distributing to members abstracts of the papers to be presented, in advance of the national meetings.

3. Arranging for National Symposia on organic chemistry. These are held every two years and the speakers and program are determined by the members of the Organic Division.

4. Establishing and promoting policies vital to the advancement of organic chemistry.

If you wish to become a regular member of the Organic Division, all that is necessary is to give or send your name, mail address and $1.50 to:

RALPH W. BOST, *Secretary*

Department of Chemistry
University of North Carolina
Chapel Hill, North Carolina

HETEROCYCLIC CARBONIUM SALTS

Ralph L. Shriner

(With Richard Otter, Paul Vogel, Hugh Johnston,
Edward Howard and Calvin Wolf)

Previous studies indicated that from a
chemical point of view, benzopyrylium salts could
be represented by the two resonating allylic
cationic structures, Ia and Ib.
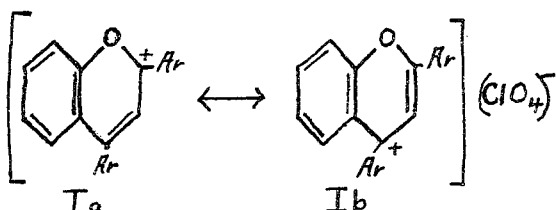
One of the methods used for the synthesis
of substituted benzopyrylium salts consists in
treating a chromone (II) with a Grignard reagent to
produce a carbinol which is then treated with
perchloric acid to produce the salt, Ia↔Ib.
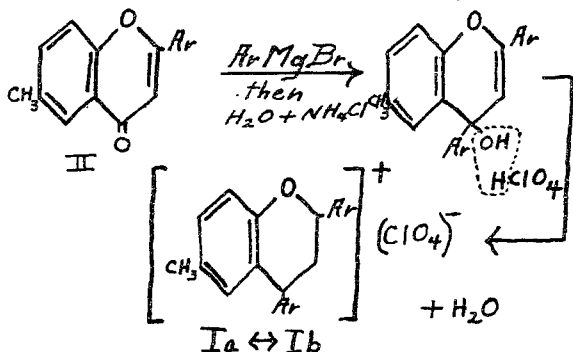
It has now been found that such salts can be made
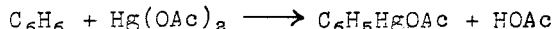from a chromanone (III) by the following reactions:-

THE MECHANISM OF THE MERCURATION OF BENZENE
F. H. Westheimer
with William Klapproth and R. M. Schramm

Anion Catalysis

The mercuration of benzene by mercuric acetate.

$$C_6H_6 + Hg(OAc)_2 \longrightarrow C_6H_5HgOAc + HOAc$$

was discovered in 1898. It has recently been shown
(J. Am. Chem. Soc., 69, 773 (1947)) that the mercur-
ation with mercuric nitrate in 50% nitric acid
(freed from oxides of nitrogen by urea) is much more
rapid than mercuration in more dilute nitric acid
solution or mercuration by mercuric acetate.

$$C_6H_6 + Hg(NO_3)_2 \longrightarrow C_6H_5HgONO_2 + HNO_3$$
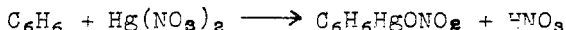
In the course of the present investigation, it was
shown that mercuration is catalyzed by anions such
as NO_3^-, ClO_4^-, HSO_4^-. The rates of mercuration of
benzene with solutions of nitrates and perchlorates
are shown below.
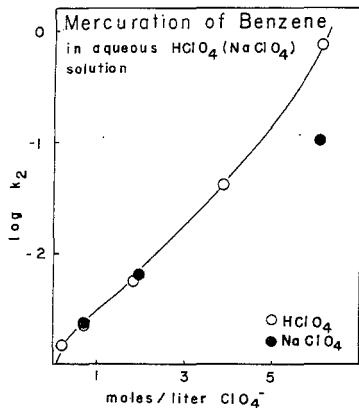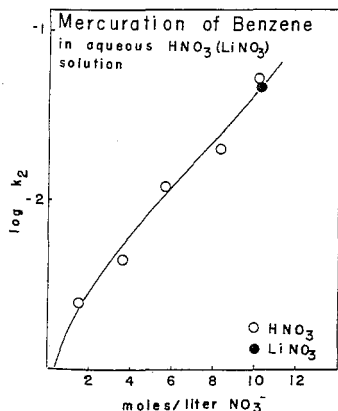
Since the second order rate constant is as
great for $LiNO_3$ as for HNO_3, it is clear that the
NO_3^- ion, not the H^+ ion is the true catalyst.
Apparently the active mercurating agent is $Hg(NO_3)^+$
(or $Hg(ClO_4)^+$) yet the rate of mercuration in solu-
tions of Cl^- (with which Hg^{++} complexes strongly)
is nil.

CONFIGURATIONAL RELATIONSHIPS AND CONFIGURATIONAL STANDARDS

M. L. Wolfrom

Introduction

A great many misconceptions and incorrect practices have arisen among present day organic chemists in treating optically active compounds. This is due mainly to the fact that the problems concerned were not settled by Vant Hoff and Emil Fischer in their time and later workers have not always been in agreement nor have they always clearly understood the fundamental nature of the phenomena with which they were dealing. It would seem appropriate to review the present status of this question and to formulate points upon which common agreement should be feasible and explicit.

Elements of symmetry

These elements, long known to the crystallographers, may well be brought into review. They are the following.
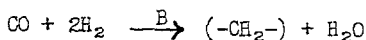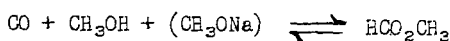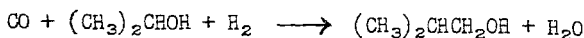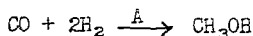
Center of symmetry
Axes of symmetry
Rotating
Alternating
Plane of symmetry

A center of symmetry always has associated with it an alternating axis of symmetry but an alternating axis of symmetry may exist without a center of symmetry. When a three-dimensional figure possesses an alternating axis of symmetry or a plane of symmetry, the mirror image of the object can be brought into identity with the object and a molecule which has such a model will be optically inactive. A rotating axis of symmetry is not critical for optical activity and the model of an optically active molecule may posses such an element; in this case substituent positions, for acyclic compounds, equidistant from such an axis will be chemically equivalent.

It is thus apparent that an optically active

CATALYSIS OF HYDROFORMYLATION AND OTHER REACTIONS

by Homer Adkins

Carbonylations

$$CO + 2H_2 \xrightarrow{A} CH_3OH$$

$$CO + (CH_3)_2CHOH + H_2 \longrightarrow (CH_3)_2CHCH_2OH + H_2O$$

$$CO + CH_3OH + (CH_3ONa) \rightleftharpoons HCO_2CH_3$$

$$CO + 2H_2 \xrightarrow{B} (-CH_2-) + H_2O$$

A. at 375-400^C and 3000 p.s.i. over $ZnO \cdot ZnCr_2O_4$
B. at 180-200^C and 15-150 p.s.i. over $Co \cdot ThO_2 \cdot MgO \cdot kiesel$.

Reppe Acrylate Process

$$HC{\equiv}CH + CO + CH_3OH \xrightarrow[HCl]{Ni(CO)_4} CH_2{=}CHCO_2CH_3$$

$$4HC{\equiv}CH + Ni(CO)_4 + 4CH_3OH + 2HCl \longrightarrow 4CH_2{=}CHCO_2CH_3$$

$$+ NiCl_2 + H_2$$

$$NiCl_2 + 2\overset{+}{NH_4} + 4CO \longrightarrow Ni(CO)_4 + 2NH_4Cl$$
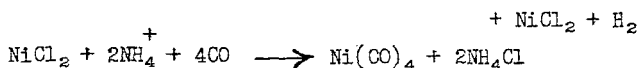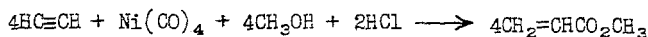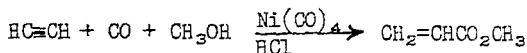
Amount of Reaction Over Various Catalysts

From	Catalyst	Temp.	Product
Butenes	$Fe_2O_3 \cdot MgO \cdot CuO \cdot K_2O$	650^C	230 Butadiene
Ethanol and Acetaldehyde	$Ta_2O_5 \cdot$ Silica Gel	340^C	64 Butadiene
$CO + 2H_2$	$Co \cdot ThO_2 \cdot MgO \cdot kiesel$	200^C	8 Hydrocarbons
$CO + 2H_2$	$Fe_3O_4 \cdot Al_2O_3 \cdot K_2O$	225^C	20-40 Hydrocarbons
Cyclohexene	Alumina	475^C	25-250 Cyclopentenes

Calculated as grams of product per liter of catalyst per hour

Cobalt Carbonyl as a Catalyst for Hydrogenation

George Krsek

$$CH_3CH=CHCHO + H_2 \longrightarrow CH_3CH_2CH_2CHO$$

$$CH_2=CHCOCH_3 + H_2 \longrightarrow CH_3CH_2COCH_3$$

$$C_6H_5CH=CHCO_2C_2H_5 + H_2 \longrightarrow C_6H_5CH_2CH_2CO_2C_2H_5$$

$$(CH_3)_2C=CHCOCH_3 + H_2 \longrightarrow (CH_3)_2CHCH_2COCH_3$$
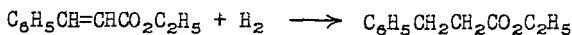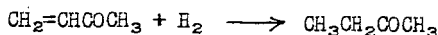
Conditions for Hydroformylation

George Krsek

30-60 g. of Unsaturated Compound

0.5-2.0 g. of Cobalt Carbonyl

30-60 ml. of Benzene or Ether or Acetone

Equal parts of carbon monoxide and hydrogen at a pressure of 1000-6000 p.s.i.

10-200 minutes at about 125° for absorption of 70-100% of theoretical, i.e. 2 moles of gases per mole of unsaturated compound.

Hydroformylations

George Krsek, Robert Turner, Jack Williams

$$CH_3CO_2CH_2CH=CH_2 \longrightarrow CH_3CO_2CH_2CH_2CH_2CHO \qquad 75\%$$

$$CH_3CH=CHCO_2C_2H_5 \longrightarrow CH_3-\overset{\overset{\displaystyle CHO}{|}}{CH}CH_2CO_2C_2H_5 \qquad 71\%$$

$$C_2H_5O_2CCH=CHCO_2C_2H_5 \longrightarrow C_2H_5O_2C\overset{\overset{\displaystyle CHO}{|}}{C}HCH_2CO_2C_2H_5 \qquad 51\%$$

$$(CH_3CO_2)_2CHCH=CH_2 \longrightarrow (CH_3CO_2)_2CHCH_2CH_2CHO \qquad 75\%$$

$$CH_2=CHCO_2C_2H_5 \longrightarrow CHOCH_2CH_2CO_2C_2H_5 \qquad 74\%$$

$$\xrightarrow[C_2H_5OH]{} (C_2H_5O)_2CH(CH_2)_2CO_2C_2H_5$$
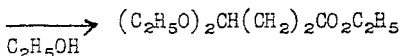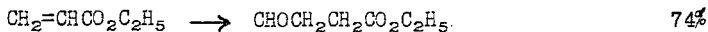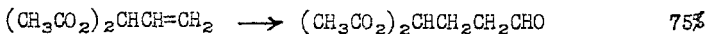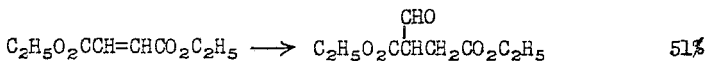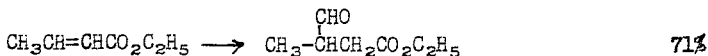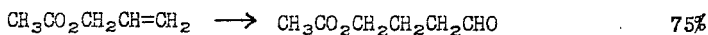
BRANCHED-CHAIN FATTY ACIDS

James Cason

During the last eight years, several groups have studied branched-chain fatty acids, chiefly because such acids have been isolated from the lipids of tubercle bacillus. The ultimate objective of the work is elucidation of the structures of the naturally-occurring acids, especially the biologically active phthioic acid, $C_{25}H_{51}CO_2H$. Preparatory to structure work in this field, synthesis and study of pure branched-chain acids is indicated. Methods used in synthesis of these acids will be outlined, and this will be followed by a discussion of methods which have been developed for locating a branching methyl group. Syntheses usually consist of two parts:
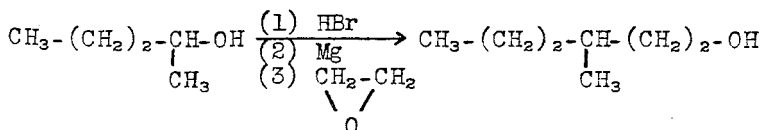
(1) Preparation of pure branched-chain alkyl halides.
(2) Extension of the appropriately branched chain to the desired length.

The most obvious method of synthesis of a branched-chain alkyl halide is extension of the chain of a secondary halide by a method such as

$$CH_3-(CH_2)_2-\underset{\underset{CH_3}{|}}{C}H-OH \quad \overset{(1) \quad HBr}{\underset{(3) \quad CH_2-CH_2}{\underset{\diagdown \diagup}{O}}{\xrightarrow{(2) \quad Mg}}} \quad CH_3-(CH_2)_2-\underset{\underset{CH_3}{|}}{C}H-(CH_2)_2-OH$$

This method is relatively unsatisfactory, however, on account of the difficulty of obtaining entirely pure secondary halides The two best methods developed for obtaining pure branched-chain halides from straight-chain starting materials are the following.

SOME ASPECTS OF STREPTOMYCIN RESEARCH

by Karl Folkers

The Clinical Limitations of Penicillin

Most of the antibiotics known in 1944 (penicillin, gramicidin, actinomycin, etc.) were found to act largely upon gram-positive bacteria.

Particularly in the case of penicillin, the activity upon gram-negative organisms was found to be highly selective and limited, or much larger quantities were needed to inhibit these bacteria.

New substances were needed which would be highly active against gram-negative bacteria, and which would not be toxic.

Discovery of Streptomycin

Streptothricin (Waksman and Woodruff, 1943) occupied a prominent place among antibiotics which act selectively against both gram-positive and gram-negative bacteria.

The search for antagonistic organisms (actinomycetes) which are active against gram-negative bacteria and which might yield antibiotic substances was started.

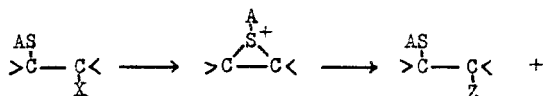Streptomyces lavendulae produces streptothricin.

Streptomyces griseus produces substance designated streptomycin - of activity against various gram-negative organisms greater than that of streptothricin (Schatz, Bugie, and Waksman, 1944). One strain came from field soil and another from a smear plate of the throat of a chicken.

During 1944-1948, nearly 1200 papers on streptomycin appeared in scientific journals.

NEIGHBORING GROUP PARTICIPATION IN SOME CHEMICAL REACTIONS

S. Winstein

Participation of Neighboring Groups in Nucleophilic Displacement Reactions

$$>\overset{AS}{\underset{X}{C}}-\overset{}{C}< \longrightarrow >C\overset{\overset{A}{\overset{+}{S}}}{\underset{}{-}}C< \longrightarrow >\overset{AS}{\underset{}{C}}-\overset{}{\underset{Z}{C}}< \quad +$$

X is Br, Cl, OTs, OH_2^+, etc.

AS is O^-, NR_2, SR

     Br, OCH_3, OAc, etc.

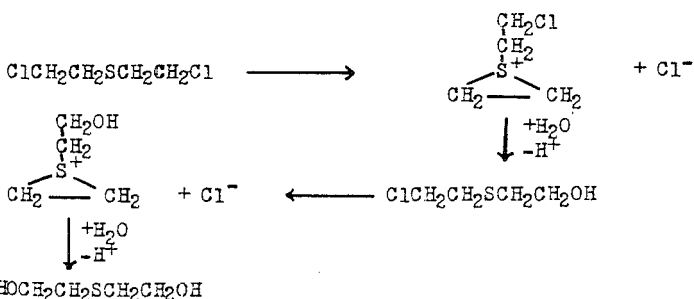$$>\overset{}{\underset{Z}{C}}-\overset{SA}{\underset{}{C}}<$$

Winstein and Buckles, J. Am. Chem. Soc., **64**, 2780 (1942)

Participation yields an intermediate cycle such as:

$$>C\overset{O}{-}C< \qquad >C\overset{\overset{R}{\overset{+}{S}}}{-}C< \qquad >C\overset{\overset{R}{\overset{+}{O}}}{-}C< \qquad >C\overset{\overset{+}{Br}}{-}C<$$

$$>C\overset{\overset{CH_3}{\overset{C}{O}}\diagup\overset{}{O^+}}{-}C<$$
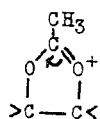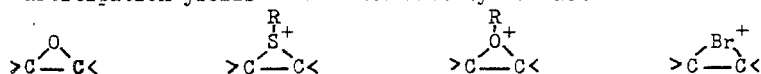
These have near analogs such as:

$R_3\overset{+}{S}$, $R_3\overset{+}{O}$, $(C_6H_5)_2I^+$,

$$R-C\overset{\overset{+}{N}\diagdown\overset{H}{\underset{H}{}}}{\underset{O-R'}{=}}$$

$$ClCH_2CH_2SCH_2CH_2Cl \longrightarrow \overset{\overset{CH_2Cl}{\overset{CH_2}{}}}{CH_2\overset{S^+}{\underbrace{}}CH_2} \quad + \; Cl^-$$

$$\downarrow \overset{+H_2O}{-H^+}$$

$$\overset{\overset{CH_2OH}{\overset{CH_2}{}}}{CH_2\overset{S^+}{\underbrace{}}CH_2} \quad + \; Cl^- \longleftarrow ClCH_2CH_2SCH_2CH_2OH$$

$$\downarrow \overset{+H_2O}{-H^+}$$

$$HOCH_2CH_2SCH_2CH_2OH$$
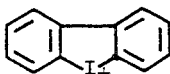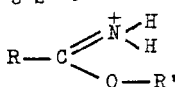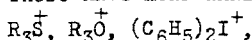
Bennett and Mosses, J. Chem. Soc., 2956 (1931)
Bartlett and Swain, Report No. 4683, Division 9, N.D.R.C., O.S.R.D.
Price, J. Org. Chem., 12, 232, 255 (1947)

THE STRUCTURE OF STRYCHNINE

R. B. WOODWARD

EVIDENCE	CONCLUSION

1. FORMS SALTS B.HX.
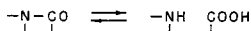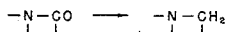   CONTAINS NO N-H GROUP
   N LOST AT 3RD STAGE OF EXHAUSTIVE
   METHYLATION

2. HYDROLYSIS GIVES AMINO ACID $C_{21}H_{24}O_3N_2$
   WHICH IS READILY RECONVERTIBLE
   TO STRYCHNINE:

$$-N-CO \rightleftharpoons -NH \quad COOH$$

   ELECTROLYTIC REDUCTION GIVES DIACIDIC
   BASE STRYCHNIDINE, $C_{21}H_{24}ON_2$:

$$-N-CO \longrightarrow -N-CH_2$$

3. CATALYTIC HYDROGENATION GIVES
   DIHYDROSTRYCHNINE, $C_{21}H_{24}O_2N_2$:

$$-C=C- \longrightarrow -CH-CH-$$
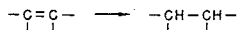
4. ULTRAVIOLET SPECTRUM IS THAT OF AN
   ACYL ANILINE

   STRYCHNIDINE HAS THE PROPERTIES OF
   A DIALKYLANILINE:

   OXIDATION GIVES OXALYLANTHRANILIC ACID

EXTRACTION

Lyman C. Craig

Collaborators - Calvin Golumbic, Harold Mighton, Elwood Titus, Byron Williamson, Yoshio Sato, Guy T. Barry and J. Delafield Gregory.

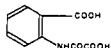Perhaps the greatest limitation of present day organic chemistry in the field of natural products and biochemistry is the problem of the separation of the complex mixtures usually involved. Even the necessary proof, prior to final identification, that a single individual compound has indeed been isolated is based on separation attempts. Since the mixtures to be fractionated are frequently of poor stability and are of molecular weight greater than a few hundred, the methods heretofore so greatly relied upon in organic chemistry such as distillation and boiling point determination or fractional crystallization and melting point determination, are frequently useless. Chromatography obviously offers great promise for the problem. However, experience has shown us the need for more than one method of fractionation preferably when entirely different physical properties form the basis of the different methods.

Extraction is one of the oldest tools of organic chemistry but has until recently been used only for crude preliminary separations or for group separations. However, for a number of reasons, it should be an ideal tool for precise separation and characterization of many substances. Some of the reasons might be listed as follows:

1. It can be accomplished under mild conditions.
2. A wide selection of solvents is now available.
3. It is ideal for small scale laboratory work.
4. The partition ratio theoretically offers a physical constant which might take the place of a melting point or boiling point.
5. Precise mathematical interpretation should be possible.
6. Partition ratios are frequently highly specific constants.

METAL COMPLEXES

T. A. Geissman

The effect of the structures of related organic chelatogenic compounds upon their ability to form complexes with copper is being examined chiefly with reference to the effect of some of these substances in biological systems. It has been found that many substances having copper-complexing ability stabilize epinephrine and prolong its action upon the isolated rabbit ileum (Clark and Geissman, Nature, 163, 36 (1949); J. Pharm. Exp. Ther., in press (1949)). The differences in activity of the compounds examined in this way made it appear that significant differences exist in their ability to neutralize the effect of copper in catalyzing epinephrine destruction by autoxidation.

A considerable amount of work by a number of investigators during the past several years is leading to an understanding of the effects of structure upon chelate stability. Chelate stability in substances of the salicylaldehyde and β-diketone type, and their anils, appears to depend upon their acidity as phenols; the effects of resonance, permitting the participation of forms involving double-bondedness in both oxygen atoms; steric effects upon such resonance; in anils, the nature of the amines involved; and the nature of the metal atom.

In the present studies, copper complexes with flavonoid substances having several different kinds of chelatogenic groupings have been examined by polarographic and spectrophotometric methods.

Among the points of interest were the effect of substituents in the aromatic nuclei of the compounds used, the degree of complexing when two chelatogenic groupings were present in the same molecule, and the relative effectiveness of chelatogenic groupings of different kinds.

Polarographic studies proved unsuitable for use in many cases, and most attention has been directed to spectral data. It was found necessary to work at high dilutions to avoid the precipitation of insoluble complexes, and it was found that in this region no marked formation of complexes of the type CuF_2 (FH and F^- are used to represent unionized and ionized chelate-forming compound) were observed. Calculations of an equilibrium constant for the reaction

$$FH + Cu^{++} \rightleftharpoons CuF^+ + H^+$$

POLYMERIZATION AND FREE RADICALS

Frank R. Mayo

There are three principal kinds of free radical reactions: addition to a double bond, transfer of an atom from a molecule to a radical, and interaction of two radicals.

$$Br\cdot + H_2C=CH-CH_3 \longrightarrow Br-CH_2-\overset{\cdot}{C}H-CH_3$$

$$Br-CH_2-\overset{\cdot}{C}H-CH_3 + HBr \longrightarrow n\text{-}PrBr + Br\cdot$$

$$H_2C=CH-CH_3 + HBr \longrightarrow n\text{-}PrBr$$

$$Ac_2O_2 \longrightarrow Me\cdot + CO_2 + AcO\cdot \text{ etc.}$$

$$Me\cdot + C_6H_5-CHMe_2 \longrightarrow MeH + C_6H_5-\overset{\cdot}{C}Me_2$$

$$2C_6H_5-CMe_2 \longrightarrow C_6H_5-CMe_2-CMe_2-C_6H_5$$
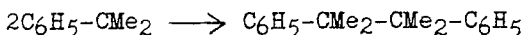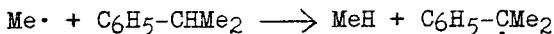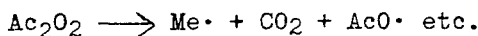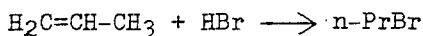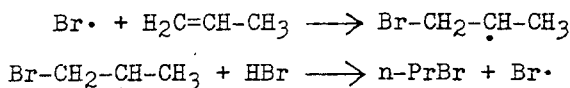
The polymerization of styrene involves the same types of reactions:

$$H_2C=C\overset{H}{\phi} + \text{Catalyst} \xrightarrow{k_i} R-CH_2-\overset{H}{\underset{\phi}{C}}\cdot$$

$$R-(CH_2-\overset{H}{\underset{\phi}{C}})\overset{\cdot}{_n} + H_2C=C\overset{H}{\phi} \xrightarrow{k_p} R-(CH_2-\overset{H}{\underset{\phi}{C}})\overset{\cdot}{_{n+1}}$$

$$R-(CH_2-\overset{H}{\underset{\phi}{C}})\overset{\cdot}{_n} + CCl_4 \xrightarrow{k_{ct}} R-(CH_2-\overset{H}{\underset{\phi}{C}})_n-Cl + Cl_3C\cdot$$

$$Cl_3C\cdot + H_2C=\overset{H}{C}-\phi \longrightarrow Cl_3C-(CH_2-\overset{H}{\underset{\phi}{C}})\cdot$$

$$R-(CH_2-\overset{H}{\underset{\phi}{C}})\overset{\cdot}{_n} + R-(CH_2-\overset{H}{\underset{\phi}{C}})\overset{\cdot}{_m} \xrightarrow{k_t} \text{non-radical products}$$