NATIONAL ACADEMY OF SCIENCES

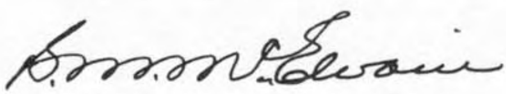
SAMUEL MARION MCELVAIN

1897—1973

A Biographical Memoir by

GILBERT STORK

Biographical Memoir



SAMUEL MARION McELVAIN

December 9, 1897–April 11, 1973

BY GILBERT STORK

S(AMUEL) M(ARION) McELVAIN was for his entire professional career a member of the chemistry department of the University of Wisconsin in Madison. That period—spanning the thirty-eight years from his appointment as instructor in 1923 (full professor from 1933) to his retirement in 1961—coincided with the explosive growth of organic chemistry. That growth resulted in no small measure from a handful of pioneers in a few universities who strove to bring some order to what was then a largely empirical field.

McElvain was one of those pioneers in the formative years of American organic chemistry. His work resulted in major contributions to the understanding of the mechanism of certain base-catalyzed reactions of esters and to the relation between structure and reactivity. It is this latter concern, together with an unusual ability to systematize these relationships, that led McElvain to what was probably his major scientific contribution, the discovery and study of the ketene acetals, a class of substances that proved to be of considerable synthetic interest, as well as of great significance with respect to the emerging theories of chemical reactivity.

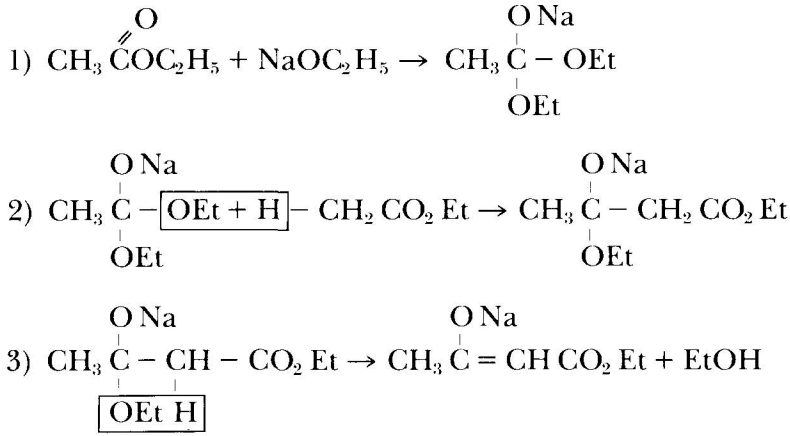
McElvain's est in relating chemical behavior to structure extended ological activity, more particularly in the field of anesthesia. This led to another major contribution,

the design of local anesthetics, some of which were developed into important and very successful drugs (Metycaine™, Surfacaine™) by the pharmaceutical house of Eli Lilly and Company.

Solomon and Eliza (Childess) McElvain had already had five children, four of whom died in infancy, when their last, Samuel Marion, was born on December 9, 1897 on a farm near DuQuoin, Illinois. The young McElvain attended the public school of DuQuoin, graduating from high school in 1915. The family then moved to St. Louis where, urged by his older brother who was a physician, McElvain enrolled in the St. Louis College of Pharmacy. Although this foray may have initiated his later interest in the design of possible anesthetics, McElvain became quickly convinced that his future lay elsewhere and, in 1916, he became a student in the Department of Chemical Engineering of Washington University in St. Louis. During his undergraduate days there, "Mac," as he had become known, partially supported himself through school by working in a drugstore during whatever spare time he had. Indeed, at the suggestion of the owner of the store, who had generously offered to pay his expenses if he should be successful, Mac traveled to Columbia, Missouri to take—and pass—the State Board examination to become a registered pharmacist. This little excursion did not, however, interfere with MacElvain's chemical career; after his graduation from Washington University in 1920, McElvain started to work toward his Ph.D. in organic chemistry at the University of Illinois under the tutelage of Roger Adams. In 1923, just three years later, he received his Ph.D. and was appointed instructor in the Chemistry Department of Wisconsin. The young instructor wasted no time starting a research program that led him over the years into a number of areas I will now discuss. I have organized this brief survey as follows: I. The Acetoacetic Ester Condensation. II. Ketene Acetals. III. Chemistry of Pyridines and Piperidines.

I. THE ACETOACETIC ESTER CONDENSATION

It may be hard for today's reader to appreciate the rather nebulous approach to chemical mechanisms at the time McElvain began his research career. One of the then widely held mechanisms for the important Claisen self-condensation of ethyl acetate (the "acetoacetic ester condensation"), which is shown below, illustrates the situation:



McElvain examined, in a number of papers published between 1929 and 1934, some of the controversies then surrounding this reaction. He was able to show, by careful quantitative experiments: 1) that although sodium metal had repeatedly been claimed to be the initiator of the condensation reaction, the initiating reagent is actually the metal alkoxide formed by various side-reactions of the metal. This suggestion had indeed been put forward very early by Claisen himself, but it had subsequently been vigorously contested, inter alia, by Arthur Michael. 2) That the "acetoacetic ester condensation" could be applied, in contrast to previous claims, to form the β-ketoesters derived from the homologs of propionic esters simply by removal of the alcohol generated in the condensation, thus driving it to completion. 3) That the previous failure to achieve the self-condensation of

esters such as ethyl isobutyrate, which only have one hydrogen alpha to the ester carbonyl, is not an intrinsic property of such esters. He concluded that such condensations might succeed if stronger bases than metal alkoxides were used, and his suggestion to Spielman and Schmidt that these self-condensations might work with mesitylmagnesium bromide indeed led to success. Hauser, independently, made the same observation, using sodium triphenylmethide as the base.

These contributions were fundamental to the development of our present understanding of base-catalyzed reactions.

II. KETENE ACETALS

McElvain's interest in ketene acetal was originally aroused by a proposal in the literature that 1,1-diethoxyethylene, the diethylacetal of ketene, is an intermediate in the above-mentioned Claisen self-condensation of ethyl acetate. McElvain's view of the course of the Claisen condensation was incompatible with this suggestion. The properties ascribed to the supposed ketene acetal seemed to him highly unlikely, and he showed that the "intermediate" that had been isolated was actually a mixture of ethanol and ethyl acetate! The postulated structure did, however, seem intriguing, and McElvain set out to synthesize the real ketene acetal. Success was reported in 1936, and over the next nineteen years McElvain published thirty-seven papers encompassing the synthesis, properties, and synthetic usefulness of this unusually reactive class of substances.

McElvain quickly recognized (1940) that the ketene acetal structure was a special case of what Robert Robinson had labeled a "heteroenoid" system and as such should exhibit especially high nucleophilicity. It is also historically and pedagogically (more about this later) noteworthy that McElvain's second and third papers on ketene acetals (J. Am. Chem.

Soc., 62:964, 1281; 1940) were among the first papers in the United States to make explicit use of the "curved arrows" introduced a few years earlier, largely by Robinson in England, to indicate the motion of electron pairs attending bond formation.

A large number of novel reactions were encountered in the study of ketene acetals for which McElvain introduced a general method of synthesis, the dealcoholation of orthoesters by means of aluminum alkoxides. The study of the unusual chemistry of these nucleophilic species was to lead to a number of surprising reactions, such as the remarkable ability of the parent substance to form carbon-carbon bonds with particularly reactive halides such as benzyl halides.

$$C_6H_5CH_2Br + H_2C=C(OEt)(OEt) \rightarrow C_6H_5CH_2CH_2C(=O)-OEt + EtBr$$

This reaction is not of great synthetic utility but has mechanistic analogies with the broad area of enamine chemistry, which was developed much later. Much more potentially useful was the reaction of ketene diethylacetal with acid chlorides, a reaction that leads to a very simple synthesis of β-ketoesters. This is shown below

$$R-C(=O)Cl + CH_2=C(OEt)(OEt) \rightarrow R-C(=O)-CH_2C(=O)-OEt + EtCl$$

and will serve to illustrate the general type of reaction undergone by ketene acetals with strong electrophiles. Note that the β-ketoester thus formed is accompanied only by the volatile ethyl chloride, and that the reaction represents a completely general synthesis of the very class of compounds that had attracted McElvain's early interest in an entirely different context (see above). Every generation is condemned to redis-

cover part of what was known to the previous one, and it is interesting that a very similar reaction has been "introduced" recently that uses a mixed ethoxy trialkylsiloxy ketene acetal in place of the more convenient ketene acetal.

III. PYRIDINE AND PIPERIDINE CHEMISTRY

McElvain's early interest in pharmacology focused on cocaine analogs during his graduate work with Roger Adams at Illinois. By the time he started independent work as an instructor at Wisconsin, McElvain was convinced that structures embodying relatively simple elements of the cocaine structure might show both enhanced anesthetic activity and lowered side effects. McElvain's first independent publication (1924) describes the synthesis of benzoates of simple N-hydroxyalkylpiperidines. It is extraordinary that it includes the substance that eventually became, after its introduction by Eli Lilly, the widely used local anesthetic Metycaine™. This marked the beginning of a long and fruitful association between McElvain and Eli Lilly.

A number of additional substances of this general type were synthesized in collaboration with Thomas P. Carney, who was a postdoctoral associate of McElvain's in 1943 and 1944 and later became a vice president of Eli Lilly. I still remember the sight on Tom Carney's laboratory bench when all of the various piperidine hydrobromides he had made on one of his last days at work were stacked to dry on pieces of filter paper held on ring stands all over the laboratory. One of these substances eventually was developed by Eli Lilly as the clinically valuable local anesthetic Surfacaine™.

Although he returned to this pharmaceutical interest in anesthetics from time to time, McElvain mostly used it to spark important fundamental research both in piperidine and in pyridine chemistry. This area, like that of ketene acetal chemistry, remained a lifelong interest that found

expression in over thirty papers. In pyridine chemistry, McElvain made important studies of the bromination and sulfonation of pyridines and introduced a number of much-improved methods for the synthesis of several of these heteroatom-substituted pyridines. He was the first to find a general synthesis of 3- and 4-piperidones by the use of the Dieckman cyclization of aminodiesters. In many cases the resulting ketones were further elaborated to potential cocaine analogs.

McElvain's involvement in piperidine chemistry, parenthetically, turned out to be of considerable interest to me: it led to my going to the University of Wisconsin for the Ph.D. because of the (correct) surmise that McElvain might show some sympathetic interest in my planned use of 4-piperidones in a quinine synthesis.

McELVAIN AS TEACHER

Important as many of McElvain's scientific contributions have proven to be, his influence as a guide of the young people who elected to work with him for the doctorate was even greater—and this influence did not confine itself to the members of his group. McElvain was an outstanding teacher, and his graduate courses were extremely successful. One was the celebrated course in qualitative organic analysis for which he wrote a successful text *The Characterization of Organic Compounds* (1945; revised edition, 1953). Many first tasted in that course the thrill of discovery and acquired the skill of putting together the pieces of a chemical detective story, of weighing the importance of conflicting clues, and of exercising their powers of logical analysis. This, of course, was all without benefit of NMR or of infrared spectroscopy and without the help of gas, liquid, or thin layer chromatography! The course relied sometimes, as any course must have at the time, on color tests of dubious generality and made use of samples of

"unknowns" that were very large by current standards. Much was learned in the course, in large part because of McElvain's insistance on clear, logical analysis.

In one other graduate course, or rather a portion of a graduate course that he shared with two other members of the organic staff, McElvain must have been one of the first to teach systematically the particular way to look at reactivity that was then called the "Electronic Theory of the English School." This referred to the analysis of the course of reactions based on an attempt at the rational prediction of the fate of electron pairs involved in bond making and breaking. The brilliant systematization Robinson had developed in an *Outline of an Electrochemical (Electronic) Theory of Organic Reactions* (1932) had been given wider circulation by the chapter written by J. R. Johnson in the first edition (1938) of Gilman's celebrated *Advanced Organic Chemistry*. This approach to chemistry was, however, far from common when McElvain started teaching it formally.

McElvain was able to project a certain avuncular sternness (everyone in his group referred to him as "Uncle Mac"). He was always accessible, his door open—but one had to have something to say. One did not drop in for casual conversation. Mac would usually be working at his desk on a manuscript that he would later turn over to Grace Legler, the organic group's secretary. He would raise one eye from his writing toward the visitor, who was expected to get to the point, unassisted. Having thus ensured that he would be spared trivialities, Mac then gave the matter his concentrated attention. Perhaps his sense of humor was even more appreciated because of this kind of aloofness. I will always remember the sudden hearty laughter with which he greeted an outraged report of my (presumed?) lack of cooperation in enforcing rigorous discipline on the undergraduates in the laboratory section in which I was a teaching assistant. He then

arranged for me to get a University Fellowship to replace the assistantship for which the powers that be had found me no longer acceptable.

It took some time for the graduate students in Mac's group to appreciate the warmth behind the projected aloofness. It became quite evident when Professor and Mrs. McElvain entertained those of his group who had remained in Madison at Thanksgiving dinners in their home. And it was with great anticipation that, on several such occasions, we walked through the snow to the house on 2017 Adams Street.

One cannot help thinking that McElvain's special ability to instill high standards and respect for hard work, his emphasis on developing responsible self-reliance, at the same time that he was able to make his students aware of his genuine interest in their problems, were responsible for the remarkable fact that three of the students who received their doctorates in his group eventually won the American Chemical Society Award in Pure Chemistry. No other teacher of organic chemistry has yet equalled this record.

Professor McElvain was married in 1926 to Helen Roth of Madison. They had two daughters, Anne, who is now Mrs. William R. Frazier of Princeton, N.J., and Jane, now Mrs. Carl E. Jenkins of Bath, Ohio. I have had the good fortune to know Mrs. McElvain for many years. The cheerful enthusiasm, which I first encountered at the Thanksgiving parties I mentioned, was just as apparent when I had the honor of being McElvain Visiting Scholar in Madison in 1977.

It would seem appropriate to end this brief account of Professor McElvain's career by recording some of the more notable recognitions accorded him: he was chairman of the Organic Division of the American Chemical Society in 1945 and 1946; on the editorial board of the *Journal of the American Chemical Society,* 1946–1956; and he was elected to the National Academy of Sciences in 1949. The Regents of the

University of Wisconsin awarded him the title of Professor Emeritus when he retired early (at the age of sixty-three) in 1961.

The University of Wisconsin has recognized his leadership, which contributed so much to bringing its Chemistry Department to the front rank, his scientific accomplishments, and his loyalty to the University in a variety of ways. An Organic Symposium was held in his honor, in Madison, upon his retirement in 1961. The S. M. McElvain Professorship was created in 1972 (with Harlan Goering as its first incumbent). The S. M. McElvain Visiting Scholarship was established in 1977 and, finally, the organic laboratories in the Daniels-Matthews Chemistry Building at Wisconsin were named the Samuel M. McElvain Laboratories of Organic Chemistry at a ceremony on March 15, 1979. A great honor befitting an outstanding man.

I WISH TO EXPRESS my sincere thanks first to Mrs. McElvain, whose recent death before this could be published was a source of sadness to many, and also to professors Aaron J. Ihde and Harlan Goering who supplied me with much essential material.

PH.D. DEGREES TAKEN UNDER S. M. McELVAIN

1928 Nelson W. Bolyard, James R. Thayer
1930 Charles F. Bailey, Kenneth Crook
1931 Robert N. Isbell, Charles F. Koelsch, Joseph Semb
1932 Arthur C. Cope, Edward A. Prill, J. M. Snell, Frank M. Strong, William B. Thomas
1933 Richard F. B. Cox, Benjamin W. Howk, Sulo A. Karjala
1934 Wray V. Drake, Norman G. Fischer, Edwin H. Kroeker, Lewis A. Walter
1936 John R. Roland
1937 Fred Beyerstedt, Arthur Magnani
1938 Harry M. Barnes, Stanford Moore, Charles W. Tullock
1940 Emanuel L. Foreman
1941 Harry Cohn, Harold G. Johnson, Allan K. Schneider, Robert F. Taylor
1942 Howard B. Burkett, Donald G. Kundiger, Philip M. Walters
1944 Edward L. Engelhardt, Arthur G. Jelinek, Robert E. Kent, James W. Langston
1945 Gilbert Stork
1947 Robert L. Clarke, Kurt J. Rorig, Calvin L. Stevens
1948 Michael J. Curry, Robert E. McMahon, Everett H. Pryde, Juel P. Schroeder, John Vozzam
1949 George P. Gregory, Robert E. Lyle, Jr., John C. Safranski, Jr., Burris D. Tiffany, James T. Venerable
1950 William B. Dickinson, Paul M. Laughton, Melvin M. Olson, Bryce E. Tate, Kenneth N. Warner, Jr., Spencer H. Watkins
1951 Archibald N. Bolstad, Gerald Gilbert, Herbert F. McShane, Jr., Leo R. Morris, Wallace F. Runge
1952 Clyde L. Aldridge, Edward R. Degginer, Charles H. Stammer
1953 Loren W. Bannister, Averal T. Trimble, Jr.
1954 Robert J. ıthey, Richard S. Berger, Roy E. Starn, Jr.
1955 Edmund Eisenbraun
1956 Robert C McKay, Jr., Phillip H. Parker, Jr.
1957 Robert E Bates, David H. Clemens
1958 Rodney Clampitt, Thomas A. Lies, David C. Remy, Philip L. /eyna

POSTDOCTORAL ASSOCIATES

Paul R. Johnson (1938–1940)
Robert Bright (1940–1941)
Thomas P. Carney (1943–1944)
Luis A. Perez-Medina (1944–1945)
Raymond Mariella (1945–1946)

BIBLIOGRAPHY

ARTICLES

1923

With Roger Adams. Synthesis of a new bicyclic nitrogen ring. Isogranatanine derivatives. Preparation of an isomer of homococaine. J. Am. Chem. Soc., 45:2738–50.

With C. S. Marvel. *o*- And *p*-chlorotoluenes. Org. Synth., 3:33–35.

1924

Piperidine derivatives. A cyclic and an open-chain compound related in structure to cocaine. J. Am. Chem. Soc., 46:1721–27.

1925

Nicotinic acid. Org. Synth., 4:49–51.

1926

Piperidine derivatives. II. 1-Alkyl-3-carbethoxy-4-piperidyl benzoates. J. Am. Chem. Soc., 48:2179–85.

Piperidine derivatives. III. 1-Alkyl-3-carbethoxy-4-piperidyl *p*-amino-benzoates. J. Am. Chem. Soc., 48:2239–42.

1927

Piperidine derivatives. IV. Substituted piperidinealkyl benzoates and *p*-aminobenzoates. J. Am. Chem. Soc., 49:2835–40.

With J. R. Thayer. Piperidine derivatives. V. Preparation and reduction of certain phenyl-substituted 3-carbethoxy-4-piperidones. 1-Cyclohexyl- and 1-phenylethyl-3-carbethoxy-4-piperidyl-*p*-aminobenzoates. J. Am. Chem. Soc., 49:2862–69.

1928

With J. R. Thayer. Piperidine derivatives. VI. 3-Methylpiperidinoalkyl benzoates. J. Am. Chem. Soc., 50:3348–55.

1929

With S. Mary Elizabeth Englert. Bromination of pyridine. J. Am. Chem. Soc., 51:863–66.

With Leslie H. Andrews. γ-Pyrrolidino- and γ-pyrrolinopropyl benzoates. J. Am. Chem. Soc., 51:887–92.

With N. W. Bolyard. Piperidine derivatives. VII. 1-Alkyl-4-piperidyl benzoates and *p*-aminobenzoates. J. Am. Chem. Soc., 51:922–28.

Some observations on the acetoacetic ester condensation. J. Am. Chem. Soc., 51:3124–30.

With C. Frederick Koelsch. Reaction of ethylmagnesium bromide with epichlorohydrin. J. Am. Chem. Soc., 51:3390–94.

1930

With C. Frederick Koelsch. Reaction of various Grignard reagents with epichlorohydrin. Preparation of some new chlorohydrins. J. Am. Chem. Soc., 52:1164–69.

With C. F. Bailey. Piperidine derivatives. VIII. Substituted piperidinoalkyl benzoates. J. Am. Chem. Soc., 52:1633–40.

With C. F. Bailey. Piperidine. IX. Methylpiperidinoalkyl cinnamates. J. Am. Chem. Soc., 52:2007–10.

With Kenneth E. Crook. Piperidine derivatives. X. The phenylpiperidylcarbinols. J. Am. Chem. Soc., 52:4006–11.

With C. F. Bailey. Local anesthetics derived from quinoline and isoquinoline. J. Am. Chem. Soc., 52:4013–17.

1931

With John M. Snell. Acetoacetic ester condensation. II. Reaction of esters with sodium. J. Am. Chem. Soc., 53:750–60.

With Joseph Semb. Reaction of organic halides with piperidine. I. Alkyl bromides. J. Am. Chem. Soc., 53:690–96.

With Marguerite Kuehn. *p*-Bromoanilides of isobutyric and isovaleric acids. J. Am. Chem. Soc., 53:1173–74.

With Arthur C. Cope. *N*-Methyl-*N*-phenylalkylaminoalkyl benzoates and *p*-aminobenzoates. J. Am. Chem. Soc., 53:1587–94.

With John M. Snell. Acetoacetic ester condensation. III. Role of sodium in the condensation. J. Am. Chem. Soc., 53:2310–16.

With Glen M. Kuettel. Piperidine derivatives. XI. 3-Carbethoxy-4-piperidone and 4-piperidone hydrochloride. J. Am. Chem. Soc., 53:2692–96.

1932

With B. W. Howk. Reaction of organic halides with piperidine. II.

Certain α-bromo-β-ketonic esters. J. Am. Chem. Soc., 54: 282–89.

With John B. Dorsch. Preparation of benzoylacetic ester and some of its homologs. J. Am. Chem. Soc., 54:2960–64.

With W. B. Thomas. Deamination of ethyl β-methylaminopropionate. J. Am. Chem. Soc., 54:3295–98.

With Arthur C. Cope. Synthesis of vinylethylmalonic ester and incidental compounds. J. Am. Chem. Soc., 54:4311–19.

With Arthur C. Cope. Cleavage of disubstituted malonic esters by sodium ethoxide. J. Am. Chem. Soc., 54:4319–25.

1933

With John M. Snell. Acetoacetic ester condensation. IV. The reaction product of certain aliphatic esters and sodium ethoxide. J. Am. Chem. Soc., 55:416–21.

With John M. Snell. Further remarks on the preparation of ketene acetal. J. Am. Chem. Soc., 55:427–28.

With Elmer J. Lease. Hydroxy and bromo esters derived from the hydrogenation of certain ω-acetyl esters. J. Am. Chem. Soc., 55:806–8.

With Frank M. Strong. Piperidine derivatives. XII. Local anesthetics derived from reduction products of β-acetylpyridine. J. Am. Chem. Soc., 55:816–22.

With E. A. Prill. Cyclization of a series of ω,ω′-dicarbethoxydialkylmethylamines through the acetoacetic ester condensation. J. Am. Chem. Soc., 55:1233–41.

With W. V. Drake. Reaction of organic halides with piperidine. III. Cyclohexyl bromide and the butyl bromides. J. Am. Chem. Soc., 55:1155–58.

With Reinhold R. Briese. Acetoacetic ester condensation. V. Condensation of higher esters. J. Am. Chem. Soc., 55:1697–1700.

With John M. Snell. Butyroin. Org. Synth. 13:24–26.

With S. A. Karjala. 2-Methylpiperidinopropyl thiol- and thionbenzoates. J. Am. Chem. Soc., 55:2966–73.

With B. W. Howk. Structure of α-benzoyl α-bromo esters. J. Am. Chem. Soc., 55:3372–80.

With L. A. Walters. Piperidine derivatives. XIII. Phenyl- and phenylalkyl-substituted piperidinopropyl benzoates. J. Am. Chem. Soc., 55:4625–29.

1934

With Alvin Singer. 2,6-Dimethylpyridine. Org. Synth. 14:30–33.

With W. V. Drake. Reaction of organic halides with piperidine. IV. Bromo esters. J. Am. Chem. Soc., 56:697–700.

With S. M. Elizabeth Englert. Pyrazolones derived from the carbethoxypiperidones. J. Am. Chem. Soc., 56:700–702.

With Edwin H. Kroeker. Preparation of ethyl α-carbethoxy-α-isobutyryl-β-phenylglutarate. Some observations on the retrogression of the Michael reaction. J. Am. Chem. Soc., 56: 1171–73.

With Richard F. B. Cox and Edwin H. Kroeker. Acetoacetic ester condensation. VI. Study of the mechanism of the reaction. J. Am. Chem. Soc., 56:1173–78.

With John M. Snell. Pyridyldimethylaminopropyl benzoate. J. Am. Chem. Soc., 56:1612–14.

With L. A. Walter. Reduction of cyanides. J. Am. Chem. Soc., 56:1614–16.

With Norman Fisher. Acetoacetic ester condensation. VII. Condensation of various alkyl acetates. J. Am. Chem. Soc., 56:1766–69.

With W. B. Thomas. Acetoacetic ester condensation. VIII. The condensation of ω-piperidine esters. J. Am. Chem. Soc., 56:1806–9.

With W. V. Drake. Reaction of certain amines with ethyl β-bromopropionate and n-butyl bromide. J. Am. Chem. Soc., 56:1810–12.

With Richard F. B. Cox. Acetoacetic ester condensation. IX. Condensation of ethyl α-carbethoxy-β-phenyl-γ-isobutyrylbutyrate. J. Am. Chem. Soc., 56:2459–63.

1935

With E. Russell Meincke and Richard F. B. Cox. Cyclization of certain ethylenedimalonic esters by sodium ethoxide. J. Am. Chem. Soc., 57:1133–35.

With E. A. Prill. 1-Methyl-2-pyridone. Org. Synth., 15:41–44.

With Alvin W. Singer. Relative reactivities of certain 2- and 2,6-substituted piperidines. J. Am. Chem. Soc., 57:1135–37.

5,5-Diphenylbarbituric acid. J. Am. Chem. Soc., 57:1303–4.

With E. Russell Meincke. The acetoacetic ester condensation. X. The condensation of ethyl α-ethyl-α'-carbethoxyadipate. J. Am. Chem. Soc., 57:1443–45.

With L. A. Walter. Ethyl-2-pyridylmalonic ester. J. Am. Chem. Soc., 57:1891–92.

1936

With Frederick Beyerstedt. Preparation and properties of ketene diethylacetal. J. Am. Chem. Soc., 58:529–31.

1937

With J. R. Roland. Reaction of certain monosubstituted malonic esters and methylene dimalonic esters with sodium ethoxide. J. Am. Chem. Soc., 59:132–35.

With Richard F. B. Cox. Ethyl methylmalonate. Org. Synth., 17:56–57.

With Richard F. B. Cox. Ethyl ethoxalylpropionate. Org. Synth., 17:54–55.

With Frederick Beyerstedt. The ethyl orthohalogenoacetates and their reaction with zinc and magnesium. J. Am. Chem. Soc., 59:1273–75.

With David C. Roberts. Acetoacetic ester condensation. XI. The extent of the condensation of certain monosubstituted acetic esters. J. Am. Chem. Soc., 59:2007–8.

With Frederick Beyerstedt. Ketene acetals. II. Bromoketene diethylacetal. Observations on the reactivity of bromo- and iodoethoxyacetal. J. Am. Chem. Soc., 59:2266–68.

With Harry M. Barnes. Further observations on the condensation of benzene with alloxan. J. Am. Chem. Soc., 59:2348–51.

1938

With Arthur Magnani. Reaction of various alkyl benzoates with sodium alkoxides. J. Am. Chem. Soc., 60:813–20.

With Arthur Magnani. Ketene acetals. III. The bromination of bromoketene diethylacetal. Other halogenated ketene acetals. J. Am. Chem. Soc., 60:2210–13.

With Arthur B. Ness. Enol content of some β-keto esters. J. Am. Chem. Soc., 60:2213–15.

With John W. Alexander. Separation and identification of amines with 3-nitrophthalic anhydride. J. Am. Chem. Soc., 60:2285–87.

1939

With C. W. Tullock. Piperidine derivatives. XIV. Local anesthetics derived from α-picoline. J. Am. Chem. Soc., 61:961–64.

1940

With Paul R. Johnson and Harry M. Barnes. Ketene acetals. IV. Polymers of ketene diethylacetal. J. Am. Chem. Soc., 62:964–72.

With Arthur Magnani. Dibenzoylmethane. Org. Synth. 20:32–35.

With Alvin W. Singer. Picolinic acid hydrochloride. Org. Synth., 20:79–80.

With Harry M. Barnes and D. Kundiger. Ketene acetals. V. The reaction of ketene diethylacetal with various compounds containing an active hydrogen. J. Am. Chem. Soc., 62:1281–87.

With Philip M. Walters. Ketene acetals. VI. The preparation of ketene acetals from α-bromo orthoesters. J. Am. Chem. Soc., 62:1482–84.

With E. Leon Foreman. Reaction of organic halides with piperidine. V. Negatively substituted ethyl bromides. J. Am. Chem. Soc., 62:1435–38.

With E. Leon Foreman. Reaction of organic halides with piperidine. VI. Some branched chain β-bromo esters. J. Am. Chem. Soc., 62:1438–41.

1941

With Robert D. Bright and Paul R. Johnson. Constituents of the volatile oil of catnip. I. Nepetalic acid. Nepetalactone and related compounds. J. Am. Chem. Soc., 63:1558–63.

With Karl H. Weber. Acyl exchange between esters and 1,3-diketones and β-keto esters. J. Am. Chem. Soc., 63:2192–97.

With Harold G. Johnson. Condensation of α-picoline and quinaldine with active ketones. J. Am. Chem. Soc., 63:2213–17.

With M. A. Goese. Preparation of nicotinic acid from pyridine. J. Am. Chem. Soc., 63:2283–84.

With Robert F. Taylor. Pinacolonylbarbituric acids. J. Am. Chem. Soc., 63:2513–16.

1942

With D. Kundiger. Ketene acetals. VII. The reaction of ketene

diethylacetal with various halogen compounds and acids. J. Am. Chem. Soc., 64:254–59.

With Harry Cohen. Ketene acetals. VIII. The reaction of ketene diethylacetal with α,β-unsaturated carbonyl compounds. J. Am. Chem. Soc., 64:260–65.

With P. M. Walters. Ketene acetals. IX. Ketene dialkylacetals. J. Am. Chem. Soc., 64:1059–60.

With J. Walter Nelson. Preparation of orthoesters. J. Am. Chem. Soc., 64:1825–27.

With Philip M. Walters. Preparation and properties of certain polyethoxyethanes and their bromo derivatives. J. Am. Chem. Soc., 64:1963–65.

With Howard Burkett. (1-Alkoxyvinyl)- and (1-Alkoxyethyl)-barbituric acids. J. Am. Chem. Soc., 64:1831–36.

With Robert L. Clarke and Griffin D. Jones. Ketene acetals. X. The elimination of hydrogen bromide from the acetals of α-bromoaldehydes. Isopropyl- and n-propylketene diethylacetals. J. Am. Chem. Soc., 64:1966–69.

With Philip M. Walters and Robert D. Bright. Constituents of the volatile oil of catnip. II. The neutral components. Nepetalic anhydride. J. Am. Chem. Soc., 64:1828–31.

With Harrison I. Anthes and Sydney H. Shapiro. Ketene acetal. XI. The pyrolysis of ketene acetals and orthoesters. J. Am. Chem. Soc., 64:2525–31.

1943

With M. A. Goese. 5-Ethyl-5-(2-pyridyl)-barbituric acid. J. Am. Chem. Soc., 65:2226–27.

With M. A. Goese. Halogenation of pyridine. J. Am. Chem. Soc., 65:2227–33.

With M. A. Goese. Sulfonation of pyridine and picolines. J. Am. Chem. Soc., 65:2233–36.

With A. Jelinek. Ketene acetals. XII. Reaction of ketene diethylacetal with diazonium salts. J. Am. Chem. Soc., 65:2236–39.

With J. W. Langston. Ketene acetals. XIII. Cyclic trimerization of ketene diethylacetal by hydrogen fluoride: 1,1,3,3,5,5,-hexaethoxycyclohexane. J. Am. Chem. Soc., 65:2239–41.

With D. Kundiger. Bromoacetal. Org. Synth. 23:8–10.

With K. H. Weber. Ethyl benzoylacetate. Org. Synth. 23:35–36.

With Robert E. Kent. β-Methylglutaric acid. Org. Synth., 23:60–62.

1944

With E. L. Engelhardt. Ketene acetals. XIV. Reactions of ketene acetal with quinones. J. Am. Chem. Soc., 66:1077–83.

With J. W. Langston. Polymerization of cyclohexene with hydrogen flouride. J. Am. Chem. Soc., 66:1759–64.

1945

With Bryce E. Tate. Nitrogen analogs of the ketene acetals. J. Am. Chem. Soc., 67:202–4.

With Bernardo Fajardo-Pinzon. Ketene acetals. XV. Ketene diphenylacetal and triphenylorthoacetate. J. Am. Chem. Soc., 67:650–53.

With Bernardo Fajardo-Pinzon. The preparation and alcoholysis of phenyl iminoester hydrochlorides. J. Am. Chem. Soc., 67: 690–91.

With Arthur Jelinck and Kurt Rorig. Ethane-,1- and propane-1,3-disulfonic acids and anhydrides. J. Am. Chem. Soc., 67: 1578–81.

1946

With Gilbert Stork. Piperidine derivatives. XV. The preparation of 1-benzoyl-3-carbethoxy-4-piperidone. A synthesis of guvacine. J. Am. Chem. Soc., 68:1049–53.

With Gilbert Stork. Piperidine derivatives. XVI. C-Alkylation of 1-benzoyl-3-carbethoxy-4-piperidone. Synthesis of ethyl 3-ethyl-4-piperidylacetate (*dl*-ethyl cincholoiponate). J. Am. Chem. Soc., 68:1053–57.

With Calvin Stevens. Ketene acetals. XVI. Phenylketene diethyl- and dimethylacetals from the pyrolsis of the corresponding orthoesters. J. Am. Chem. Soc., 68:1917–21.

With R. E. Kent and Calvin Stevens. Ketene acetals. XVII. The alkylation and acylation of substituted ketene acetals. J. Am. Chem. Soc., 68:1922–25.

With Thomas P. Carney. Piperidine derivatives. XVII. Local anesthetics derived from substituted piperidinoalcohols. J. Am. Chem. Soc., 68:2592–2600.

1947

With Gilbert Stork. Preparation of ethyl β-benzylaminopropionate and benzyl-di(β-carbethoxylethyl)-amine. J. Am. Chem. Soc., 69:971–72.

With Robert L. Clarke. The preparation, alcoholysis and reduction of cyanoacetaldehyde diethylacetal. Malonaldehyde tetraethylacetal. J. Am. Chem. Soc., 69:2657–60.

With Calvin L. Stevens, Ester and orthoester formation in the alcoholysis of iminoester hydrochlorides. A proposed mechanism. J. Am. Chem. Soc., 69:2663–66.

With Robert L. Clarke. Ketene acetals. XVIII. Pentaethoxyethane and tetraethoxyethylene (diethoxyketene diethylacetal). J. Am. Chem. Soc., 69:2661–63.

With L. A. Perez-Medina and R. P. Mariella. The preparation and reactions of some polysubstituted pyridines. 2-Methyl-3-hydroxy-5-hydroxymethylpyridine (4-deshydroxymethylpyridoxin). J. Am. Chem. Soc., 69:2574–79.

With Calvin L. Stevens. A study of new approaches to α-halogenated orthoesters. J. Am. Chem. Soc., 69:2667–70.

1948

With C. L. Rose, T. P. Carney, and K. K. Chen. New piperidine derivatives as local anesthetics. Anesthesiology, 9:373–80.

With M. J. Curry. Ketene acetals. XIX. 2-Methylene-1,3-dioxolanes and 1,3-dioxanes. J. Am. Chem. Soc., 70:3781–86.

With Kurt Rorig. Piperidine derivatives. XVIII. The condensation of aromatic aldehydes with 1-methyl-4-piperidone. J. Am. Chem. Soc., 70:1820–25.

With Kurt Rorig. Piperidine derivatives. XIX. Esters of substituted 4-piperidinols. J. Am. Chem. Soc., 70:1826–28.

1949

With J. P. Schr der. Orthoesters and related compounds from malono- and uccinonitriles. J. Am. Chem. Soc., 71:40–46.

With J. P. Schr der. Ketene acetals. XX. The preparation and properties o yanoketene acetals. Some novel benzylation reactions. J. A Chem. Soc., 71:47–53.

With E. H. Pryde. 2,2,5,5-Tetramethylpiperazine and derivatives. J. Am. Chem. Soc., 71:326–31.

With John F. Vozza. Piperidine derivatives. XX. The preparation and reactions of 1-methyl-3-piperidone. J. Am. Chem. Soc., 71:896–900.

With Robert E. McMahon. Piperidine derivatives. XXI. 4-Piperidone, 4-piperidinol and certain of their derivatives. J. Am. Chem. Soc., 71:901–6.

The ketene acetals. Chem. Rev., 45:453–92.

1950

With R. E. Lyle, Jr. Piperidine derivatives. XXII. Condensation of 1-methyl-4-piperidone with active methyl compounds. J. Am. Chem. Soc., 72:384–89.

With J. C. Safransky, Jr. Piperidine derivatives. XXIII. 1-methyl-4-phenylpiperidines and related compounds. J. Am. Chem. Soc., 72:3134–38.

With J. T. Venerable. Ketene acetals. XXI. Dealcoholation of orthoesters—dimethylketene dimethylacetal. J. Am. Chem. Soc., 72:1661–69.

With J. C. Safransky, Jr. Bromo derivatives of 1-methyl-3-carbethoxy-4-piperidone. J. Am. Chem. Soc., 72:3295.

1951

With Leo R. Morris. Ketene acetals. XXII. Diethoxymethylketene dimethyl acetal. J. Am. Chem. Soc., 73:206–7.

With Paul M. Laughton. Piperidine derivatives. XXIV.
1-methyl-4-phenyl-3-piperidone and related products. J. Am. Chem. Soc., 73:448–52.

With Wm. R. Davie. Ketene acetals. XXIII. Dealcoholation of orthoesters with aluminum *tert*-butoxide. J. Am. Chem. Soc., 73:1400–1402.

With A. N. Bolstad. Ketene acetals. XXIV. Preparation and properties of ketene divinyl acetal and related compounds. J. Am. Chem. Soc., 73:1988–92.

With Bryce E. Tate. The thermal decomposition of iminoester salts and the cleavage of orthoesters by these salts. J. Am. Chem. Soc., 73:2233–38.

With Bryce E. Tate. The alcoholysis of diethyl diiminomalonate

monohydrochloride. Some new pyrimidines. J. Am. Chem. Soc., 73:2760–64.

With Stanley B. Mirviss and Calvin L. Stevens. Ketene acetals. XXV. Diphenylketene dimethyl acetal. J. Am. Chem. Soc., 73: 3807–11.

With Melvin M. Olson. Base-induced reactions of certain benzyl esters. J. Am. Chem. Soc., 73:4824–27.

1952

With Henry J. Schneider and Homer Adkins. The hydrogenation of amides and ammonium salts. The transalkylation of tertiary amines. J. Am. Chem. Soc., 74:4287–90.

With Richard D. Mullineaux. Ketene acetals. XXVI. The preparation and properties of some ω-cyanoalkylketene acetals. J. Am. Chem. Soc., 74:1811–16.

With Wm. R. Davie. Ketene acetals. XXVII. The bromination of various ketene acetals. J. Am. Chem. Soc., 74:1816–21.

With Leo R. Morris. Ketene acetals. XXVIII. The dehalogenation of α,α-dibromoacetals. Isopropenylketene diethylacetral. J. Am. Chem. Soc., 74:2657–62.

With Herbert F. McShane, Jr. Ketene acetals. XXIX. Mechanism of the reaction of ketene acetal with various halides. J. Am. Chem. Soc., 74:2662–67.

1953

With Charles H. Stammer. Some reactions of 1,2-diethoxyethylene and its bromo derivative. J. Am. Chem. Soc., 75:2154–58.

With Clyde L. Aldridge. Ketene acetals. XXX. Alkylation of dimethylketene dimethylacetal. J. Am. Chem. Soc., 75:3987–93.

With Clyde L. Aldridge. Ketene acetals. XXXI. Dimethylketene ethyleneacetal. J. Am. Chem. Soc., 75:3993–96.

1954

With E. J. Eisenbraun and B. F. Aycock. Some observations on the C-methyl determination. J. Am. Chem. Soc., 76:607–9.

With Loren W. Bannister. 1,4-Diazabicyclo [2.2.2] octanes and 1,5-diazabicyclo[3.2.2.] nonanes from piperazines and homopiperazines. J. Am. Chem. Soc., 76:1126–37.

With William B. Dickinson and Robert J. Athey. Piperidine deriva-

tives. XXV. The reaction of certain 3-substituted 1-methyl-4-piperidones with organometallic compounds. J. Am. Chem. Soc., 76:5625–33.

With Edward R. Degginger and John D. Behn. Ketene acetals. XXXII. The condensation of ketene dimethyl acetal with various aldehydes and ketones. J. Am. Chem. Soc., 76:5736–39.

1955

With P. Harold Parker, Jr. Piperidine derivatives. XXVI. 1-methyl-3-benzylidene-4-piperidone dimer. J. Am. Chem. Soc., 77:492–93.

With E. J. Eisenbraun. The constituents of the volatile oil of catnip. III. The structure of nepetalic acid and related compounds. J. Am. Chem. Soc., 77:1599–605.

With Richard S. Berger. Piperidine derivatives. XXVII. The condensation of 4-piperidones and piperidinols with phenols. J. Am. Chem. Soc., 77:2848–50.

With E. J. Eisenbraun. Configuration of 3-methylcyclopentanones and related compounds. J. Am. Chem. Soc., 77:3383–84.

With W. L. McLeish. Ketene acetals. XXXIII. The addition of halogens and cyanogen compounds to methyl ketene diethyl acetal. J. Am. Chem. Soc., 77:3786–89.

With R. E. Statur, Jr. Ketene acetals. XXXIV. Tetra- and pentamethylene ketene acetals. J. Am. Chem. Soc., 77:4571–77.

With G. Robert McKay, Jr. Ketene acetals. XXXV. Cyclic ketene acetals and orthoesters from 2,2-dimethoxy-2,3-dihydropyran. J. Am. Chem. Soc., 77:5601–6.

1956

With Martin D. Barnett. Piperidine derivatives. XXVIII. 1-Methyl-3-alkyl-4-phenyl-4-acyloxypiperidines. J. Am. Chem. Soc., 78:3140–43.

With P. Harold Parker, Jr. Piperidine derivatives. XXIX. Octa- and decahydroisoquinolines from 1-methyl-3-carbethoxy-4-piperidone. J. Am. Chem. Soc., 78:5312–14.

With G. Robert McKay, Jr. Ketene acetals. XXXVI. The preparation and properties of acylketene acetals. J. Am. Chem. Soc., 78:6086–91.

1957

With E. J. Eisenbraun. Interconversion of nepetalic acid and isoiridomyrmecin (Iridolactone). J. Org. Chem., 22:976–77.

1958

With David H. Clemens. Piperidine derivatives. XXX. 1,4-Dialkyl-4-arylpiperidines. J. Am. Chem. Soc., 80:3915–23.

1959

With David H. Clemens. Ethyl (1-phenylethylidene) cyanoacetate. Org. Synth., 39:25–26.

With David H. Clemens. β-Methyl-β-phenylglutaric acid. Org. Synth. 39:54–55.

With Philip L. Weyna. Ketene acetals. XXXVII. Cyclopropanone acetals from ketene acetals and carbenes. J. Am. Chem. Soc., 81:2579–88.

With Rodney B. Clampitt. The reaction of 2-substituted cyclohexanones with organometallic compounds. J. Am. Chem. Soc., 81:5590–98.

1960

With Thomas A. Lies. 2,2,5,5-Tetramethyl-1,4-diazabicyclo[2.2.2.] octane methochloride. J. Am. Chem. Soc., 82:164–69.

With David C. Remy. Piperidine derivatives. XXXI. Certain 6-oxooctahydro- and decahydroisoquinolines and related compounds. J. Am. Chem. Soc., 82:3960–66.

With David C. Remy. Piperidine derivatives. XXXII. Reaction of 1-acyl-4-piperidones with organometallic compounds. J. Am. Chem. Soc., 82:3966–70.

BOOKS

1925

With Homer Adkins. *Practice of Organic Chemistry in the Laboratory.* New York: McGraw-Hill Book Co.

1928

With Homer Adkins. *Elementary Organic Chemistry.* New York: McGraw-Hill Book Co.

1933

With Homer Adkins. *An Introduction to the Practice of Organic Chemistry in the Laboratory*, 2d ed. rev. New York: McGraw-Hill Book Co.

1940

With Homer Adkins and M. W. Klein. *An Introduction to the Practice of Organic Chemistry in the Laboratory*, 3d ed. New York: McGraw-Hill Book Co.

1945

The Characterization of Organic Compounds. New York: The Macmillan Co.

1953

The Characterization of Organic Compounds, rev. ed. New York: The Macmillan Co.

PATENTS

1929

U.S. Patent 1,714,180 (May 21, 1929). Piperidine Derivatives.

1930

U.S. Patent 1,784,903 (Dec. 16, 1930). Piperidine Derivatives (local anesthetics).

1935

U.S. Patent 1,997,828 (April 16, 1935). Piperidine Derivatives.

1946

U.S. Patent 2,394,195 (Feb. 5, 1946). With Howard Burkett. Barbituric Compounds.

1947

U.S. Patent 2,415,897 (April 15, 1947). With Howard Burkett. Barbituric Compounds.

1947

U.S. Patent 2,418,977 (April 15, 1947). With Melvin A. Goese. Production of Bromopyridines.

1948

U.S. Patent 2,439,818 (April 20, 1948). With Thomas P. Carney. Substituted Esters of Benzoic Acid.

U.S. Patent 2,448,996 (Sept. 7, 1948). With Thomas P. Carney. 3-(2′ Methylpiperidino)-propyl p-n-Butoxybenzoate and Acid Addition Salts Thereof.

U.S. Patent 2,448,997 (Sept. 7, 1948). With Thomas P. Carney. Piperidine Propanol Esters of Phenylacetic Acid.

U.S. Patent 2,448 98 (Sept. 7, 1948). With Thomas P. Carney. 3-(2′,6′-Dimeth lpiperidino)-propyl Salicylate and Acid Salts Thereof.

1949

U.S. Patent 2,463 89 (March 8, 1949). With Gilbert Stork. The Preparation of cylated Aminoesters.

1959

U.S. Patent 2,892,842 (June 30, 1959). 4-(m-Hydroxyphenyl) Piperidines.

1960

British Patent 853,814 (Nov. 9, 1960). Piperidine Compounds.