Pergamon

Tetrahedron 55 (1999) 7391–7404

TETRAHEDRON

TETRAHEDRON PERSPECTIVE NUMBER 6

The power of observation

Gábor B. Fodor

Department of Chemistry, West Virginia University, Morgantown, WV 26506-6045, USA

Abstract

The critical role that observation can play in solving scientific problems is illustrated with several examples.

In the twentieth century, especially in the latter half, organic chemistry has become an increasingly exact science. The elucidation of the structure of a complex molecule, traditionally an extremely arduous task, has been greatly accelerated by the advent of new, potent methods of separation and analysis. Powerful new chromatographic methods allow the rapid isolation of pure compounds. The synergistic use of spectroscopic methods (especially nuclear magnetic resonance and mass spectroscopy) has largely eliminated the need for tedious chemical degradations. The rapid assignment of structure now possible has greatly promoted synthetic chemistry and the development of new synthetic methods. New theories have also given impetus to the development of organic chemistry. In the nineteenth century, the accumulation of many facts led inductively to the original theory of structure. The observation of optical activity of certain organic compounds in solution led to Pasteur's separation of antipodes and then to the tetrahedral carbon theory of Le Bel and van't Hoff. Our century is perhaps even more rich in important new theories that have led to major gains in the quality of knowledge embodied in organic chemistry. For example, the contributions of Lapworth, Robinson and Ingold to the electronic theory of organic molecules and their reactions allowed for the first time the application of deduction instead of induction in organic chemistry, as in the prediction of new reactions based on theory. The theory of resonance developed by Pauling and Wheland provided a basis for explaining many properties of molecules. Barton introduced a new theory which allowed the prediction of chemical reactivity based on molecular conformation — the beginning of modern conformational analysis. Based on arguments relating to the symmetry of molecular orbitals, Woodward and Hoffman derived a theory and rules to predict chemical reactivity (or lack of it) in a wide variety of organic reactions. In crediting the great importance of these theories, as well as others, we should recognize that they have invariably been based on critical observations and that observation of both expected and unexpected results still remains a powerful tool of the organic chemist.

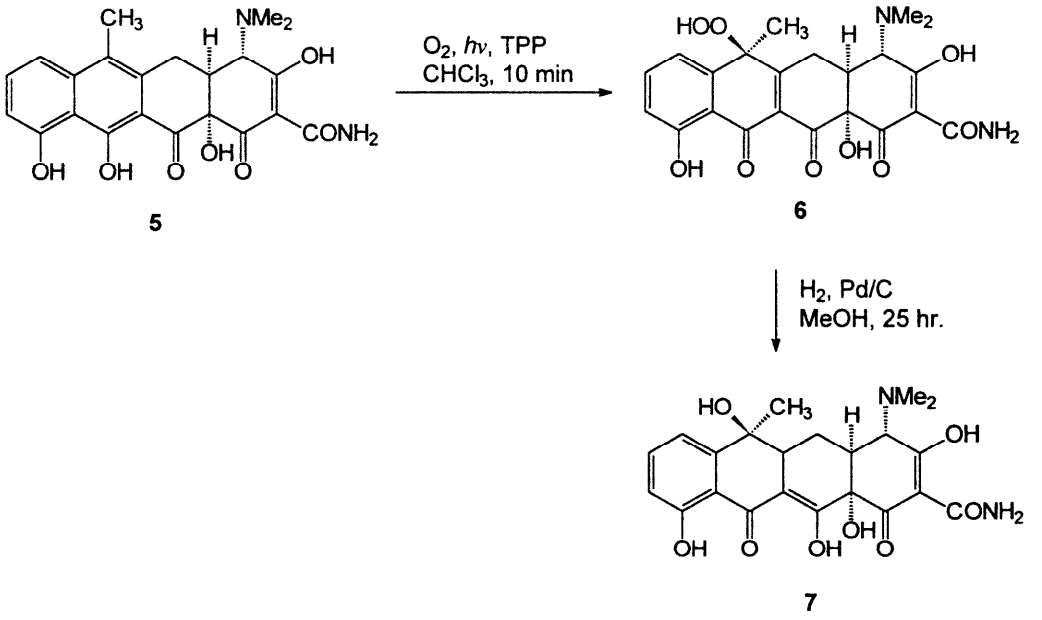
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00026-5

1. Examples of unexpected observations

For many years people had known that eating citrus fruits prevented scurvy, but all attempts to isolate the active anti-scurvy agent (vitamin C) had failed. In his studies of the adrenal cortex of the ox, Albert Szent-Györgyi succeeded in isolating small quantities of a crystalline sugar-like substance which he named hexuronic acid. This compound was a potent reducing agent that reduced silver nitrate and gave a distinctive color test with orcinol and ferric chloride; most significantly, it proved to have anti-scurvy activity.[1] Unfortunately, the quantities isolated were too small for detailed chemical and biological studies. However, at a dinner, Szent-Györgyi was served fresh green peppers, a staple in Hungary. After cutting the peppers with a steel knife (fortunately, at the time stainless-steel knives were not available), Szent-Györgyi observed on the edge of the blade the same coloration he obtained from hexuronic acid and ferric chloride, suggesting to him to look for hexuronic acid in peppers. The next day he pressed several kilograms of green peppers, yielding juice which gave a strong color test with ferric chloride. Careful processing of the juice led to the isolation of a substantial quantity of the crystalline vitamin. (Ultimately several kilograms were obtained.) A sufficient amount was then sent to W. Norman Haworth to enable him to elucidate the structure of vitamin C. Both scientists received the Nobel Prize in 1937. Thus a chance observation by Szent-Györgyi of a characteristic color was put to good use, greatly promoting research on a crucial vitamin.

Cope and coworkers had prepared a variety of (dialkylyvinyl)-alkylcyanoacetic esters which were stable to purification by distillation. However, ethyl (1-methylpropenyl)-allyl cyanoacetate (**1**) which was unchanged by distillation at 1 mm, underwent an increase[2] in both boiling point and refractive index upon distillation at 16 mm. These unexpected increases suggested to Cope that compound (**1**) was undergoing a thermally induced change to a new compound. Indeed, prolonged heating of compound (**1**) caused the complete conversion of compound (**1**) into a higher-boiling isomer. The increase in refractive index indicated to Cope that the new isomer was conjugated. Both degradation and synthesis showed that the new isomer had structure (**2**). Cope then postulated a cyclic mechanism for this isomerization which he established with further studies (Scheme 1). Today the Cope rearrangement is a widely utilized and intensively studied reaction. A critical observation by a perceptive investigator led to its discovery.

Another example of a sharp observation of the unexpected was made by R. B. Woodward[3] at a critical



Scheme 3.

2. Chemistry in the melting point tube

Theoretical knowledge and modern physical methods now enable the organic chemist to answer questions of structure in a very short time, much shorter than before. Yet organic chemistry reached today's peak by the innumerable experimental efforts that have been developed in order to promote science and answer the most delicate structural questions, even before the advent of modern instruments. How did this happen?

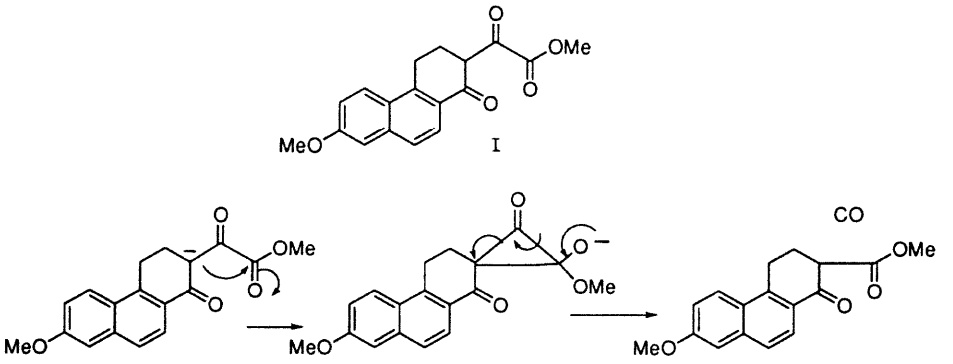
The creativity of the individual researcher and the observations made in the laboratory still remain the most important parameters. In the past, there were simple organic molecules that needed to be investigated for one reason or another. In order to do that, this author turned very early in his scientific career to the use of physical methods. In 1936–1937 when these methods were not yet predominant in organic chemical research, he cooperated with spectroscopists on structural and mechanistic problems. One of the problems, that of the acyclic vs. ring structure of nitrones, was answered by UV spectra[5] in favor of the acyclic one.

However, the great majority of the work that this author has achieved attests mostly to the power of observation combined with some imagination. Today's student hardly uses a melting point determination as it was used in the past to characterize and identify substances.

In this connection I would like to call attention to an early classic example of the significance of a melting point determination. This is found in the case of the oxalyl derivative I, prepared during the equilenin synthesis of Bachmann, Cole and Wilds.[37] In the words of a referee:

> "the crucial tricyclic intermediate β-keto ester was only achieved, via decarbonylation of the oxalyl precursor (I)... Wilds observed that when the melting point (of I) was taken in a soft glass (!) tube, decomposition was apparent, in contrast to the melting point in pyrex. Addition of powdered soft glass to the decarbonylation reaction made it successful, and the synthesis marched on."

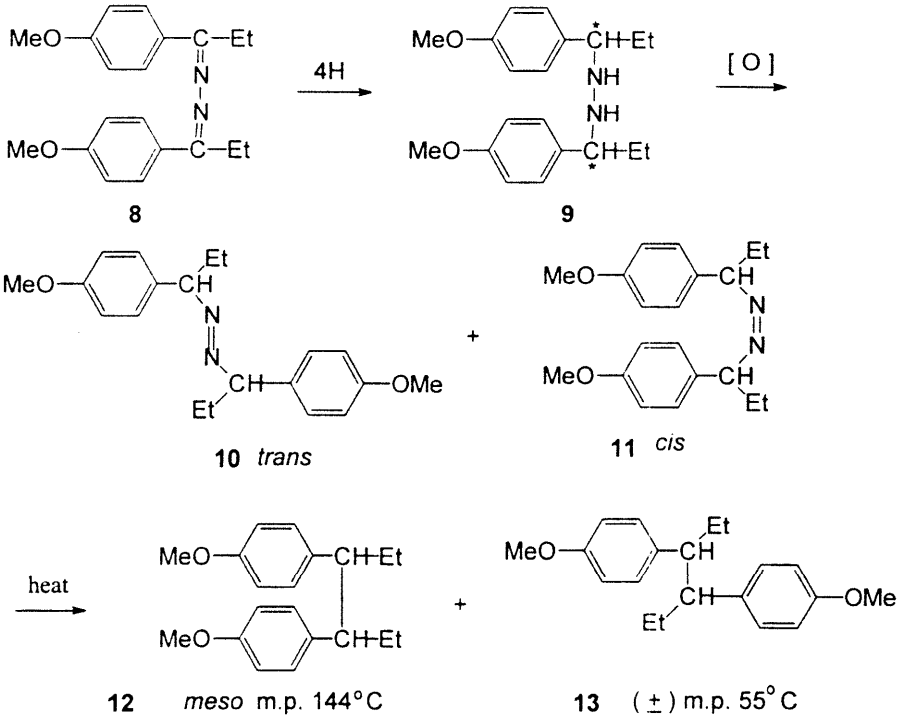
Here the loss of CO must plausibly have taken place under alkaline conditions as illustrated below.



During my career, the melting point tube and melting point determination — the observation of what is happening to the micro amount of crystals in the melting point tube — helped me to recognize a number of chemical transformations and to elucidate the structures of the products. Chronologically, the first example occurred in research directed towards the synthesis of diethylstilbestrol. These efforts were undertaken in the Laboratory of the Chinoin Pharmaceutical Company, in Budapest, during World War II. The research focused on developing a method to synthesize diethylstibestrol independently of the previously described approaches. The author's first idea was to try a thermolysis of the azine of *p*-methoxypropiophenone (**8**), to obtain diethylstilbestrol methylether in one step by an electron pairing of the two radicals that would arise by the loss of nitrogen. But this approach failed.† Azines are very stable compounds; they have high melting points and the pyrolytic conditions were too harsh to achieve any clear transformation in the sense we wanted. Therefore, we hydrogenated the azine into the corresponding hydrazine (**9**). The oil we obtained was allowed to stand in air, whereby it became crystalline. Upon fractional crystallization, two crops were obtained with melting points 75–77°C and 58–65°C, respectively. In the melting point tube both showed an interesting behavior: the main crop melted sharply at 75–77°C, and upon further heating it resolidified and gave a second melting point around 140°C. A large sample was then heated: recrystallization gave a first crop, melting point 144°C, and a second, melting point 55°C. This result was interpreted[6,7] to indicate that the hydrazine derivative (**9**) had been oxidized by air into the aliphatic azo compounds (**10**) and (**11**) which then underwent thermal decomposition with loss of nitrogen. The radicals formed then coupled to give a mixture of *meso* and racemic *p,p'*-dimethoxy-3,4-diphenyl hexanes (**12**) and (**13**) (Scheme 4). (The stereoisomeric structure of the azo compounds was confirmed in 1943 by UV spectroscopy, showing the N=N chromophore at 358 mμ. These were probably the first aliphatic azo compounds studied by UV spectra.[8]) By coincidence, on the day our thermolysis results were obtained, we received the August 1939 issue of *The Lancet* (it reached Hungary on December 1) and learned that heating anethole (*p*-1-propenylanisole) with hydriodic acid gave small amounts of impure 3,4-di-*p*-hydroxyphenylhexane.[9] Remethylation of this diphenol gave[10,11] a dimethylether of melting point 144°C, which was the same as the 3,4-di-*p*-methoxyphenylhexane we had prepared. Moreover, demethylation of our thermolysis product (with methanolic potassium hydroxide) also gave *meso*‡ 3,4-di-*p*-hydroxyphenylhexane, a compound which proved to be a new potent estrogen,[9] named 'hexoestrol', superior to the stilbestrol that we originally intended to synthesize. Thus our observation of an interesting melting point behavior led to a practical synthetic route to a compound of pharmaceutical value[13] as a synthetic estrogen.

† Now, this might be feasible by flash photolysis.

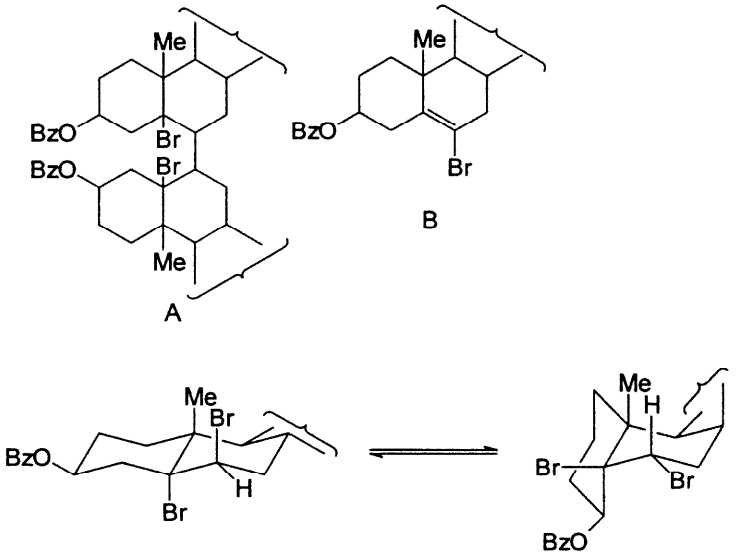
‡ Crowfoot and Carlisle established the *meso* structural assignments by X-ray crystallography.[12]



Scheme 4.

A second example where the melting point tube was to help clear up a mystery that existed in organic chemistry for about 50–60 years, was the case of the structure of steroid-5,6-dibromides. Today it may sound odd that the scientific world debated for about 60 years whether the product of the bromination of cholesteryl benzoate, a beautifully crystalline material with a melting point of 134°C and $[\alpha]_D^{20}=-39°$, was a dibromodicholestanyl dibenzoate or a monomeric monobromide (**A** or **B** (Scheme 5)). This author doubted both structures when his attention was directed to this problem by his supervisor, Dr. Z. Földi, with the aim of trying to oxidize the compound to get into a new realm of steroid hormones, i.e. products of degradation of the steroid side chain that might be converted into one of the known sex hormones, e.g.

dehydroandrosterone and, in turn, testosterone. Therefore, it was of major practical importance to carry out this oxidation.



Scheme 5.

It was observed originally in 1891 by Obermüller[14] that when benzoylcholesterol was brominated in carbon disulfide an amorphous material formed that by recrystallization gave a compound with a melting point of 138°C. The analysis of the bromine by the method of Carius, carried out in a sealed tube at only 120°C, gave a value calculated for monobromocholesteryl benzoate or dibromodicholestanyl dibenzoate (**A** or **B**, Scheme 5).

Dorée and Orange, 20 years later, reported[15] that there are two compounds formed in the bromination of benzoyl cholesterol. They determined the melting points to be 138°C and 169°C, respectively, and the first compound seemed to be identical with that observed by Obermüller. Therefore, they believed that one was a cholesteryl monobenzoate monobromide and the other was a dicholestanyl benzoate dibromide.

In England, Petrow[16] stated that both bromocholesterolbenzoate compounds formed, and reported a molecular weight twice as high as that expected for the cholesteryl benzoate monobromide. To add to the confusion, Petrow assigned the structure of the dibromodicholestanyl dibenzoate to the compound of melting point 138°C.

Although this author had doubts, he tried to oxidize this steroid benzoate bromide with chromic acid in glacial acetic acid. Observing the very low solubility of this benzoate in glacial acetic acid, he believed that the compound would not be oxidized at all. So after several days attempting to oxidize it as a suspension, the crystalline starting material of melting point 138°C, $[\alpha]_D^{20}=-38°$ was filtered off. Evaporation of the solvent gave crystals of a different material, with a melting point of 168°C, $[\alpha]_D^{20}=+64°$. This melting point was similar to that of the second compound that Dorée and Orange[15] had described. Dr. F. Wessel of the Analytical Laboratory at Chinoin subjected the compound to bromine determination, carrying out the Carius determination in a sealed tube at 300°C (not at 120°C as attempted previously). This (proper) method gave a bromine percentage exactly as calculated for benzoylcholesteroldibromide: the same result was found for the starting material, melting point 138°C. These data eliminated both structures **A** and **B** from further consideration. The author made a careful melting point determination of the lower melting isomer and found that by slowly heating it

above the melting point it resolidified to melt ultimately at 168°C. He concluded that both the starting material and the higher melting product are stereoisomeric dibromides of benzoyl cholesterol. Since this transformation could also be achieved with the higher melting, dextrorotatory isomer (the resolidified melt gave both isomers) the process proved reversible, and since it was accompanied by a change of the sign of optical rotation, the author named it 'mutarotation'. Thus, melting point determination, optical rotation and the correct analysis helped to dispel a myth that existed in the literature for over 50 years.[17] The inappropriate analysis of bromine and an incorrect molecular weight resulted in a false structural assignment, i.e. a false molecular formula. This mutarotation helped us to obtain the hitherto unknown dextrorotatory diastereomer by melting levorotatory cholesterylacetate dibromide. The new isomer was much more soluble in glacial acetic acid and therefore it could be oxidized in homogenous solution in very good yield to give acetyldehydroandrosterone dibromide. The latter dibromide, in turn, was debrominated and deacetylated in the usual fashion to give the hormone dehydroandrosterone.§

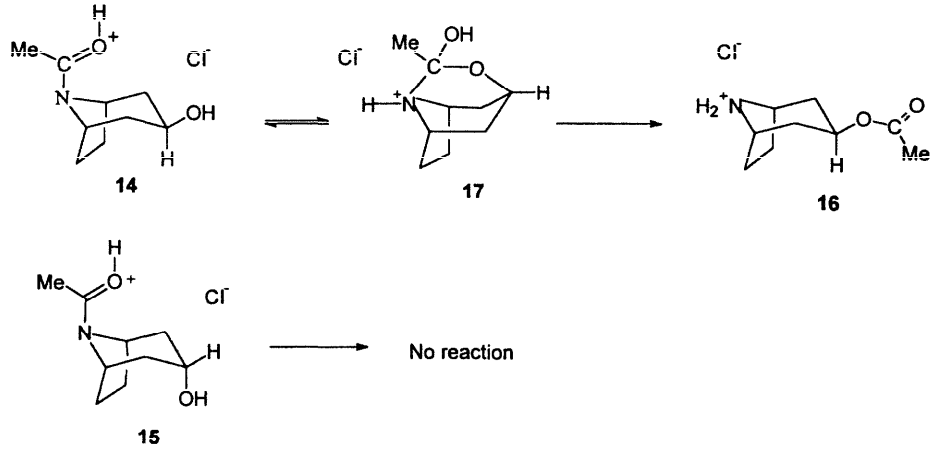
From a scientific point of view, the recognition of the mutarotation of benzoyl cholesterol dibromides led to recognition of the stereoisomerization of the two dibromides. By polarimetry an equilibrium of 79% dextrorotatory and 21% levorotatory form was established. This interconversion was studied in different solvents polarimetrically and the same phenomenon was described in more detail in *Hungarica Acta Chimica*,[18] an article that called the attention of Saul Winstein and Derek Barton to this problem.

This surprising equilibration was interpreted by Winstein and Grob[19] as an example of neighboring group participation via the intermediate formation of a cyclic bromonium bromide. Barton[20,27] saw it as an example where the diaxial kinetic product is converted, most likely via the bromonium ion, into the thermodynamically more stable diequatorial form, i.e. 5,6-dibromocoprostanyl benzoate. This result was used by Barton as an interesting example in establishing conformational theory. In this case the relative stability of the rings, cholestane versus coprostane, is reversed because the cholestane derivative is diaxial while the coprostane derivative that arises from equilibration is the diequatorial dibromo product (Scheme 5). The conclusion is that a new phenomenon — equilibration of diastereomers — was discovered basically by the observation of the resolidifying of the melt of the lower melting bromide. Finally, we note that monobromocholesteryl benzoate and dibromodicholestanyl dibenzoate were both non-existent and over 50 years of errors could have been eliminated by correct observations.

A third example of the observation of an important transformation in a melting point tube happened in 1952 when this author succeeded in establishing the (then unknown) *syn/anti*-configurations of the 3-tropanols, tropine and pseudotropine. The crucial experiment involved the *N*-acetyl derivatives of nortropine and norpseudotropine (**14** and **15**). Both amides gave crystalline amide hydrochlorides which were typical strong acids (their aqueous solutions gave free HCl which was titrated potentiometrically). The already known *N*-acetylnortropine hydrochloride[21] melted at ca. 100°C to give a transparent melt which did not change upon further heating. In sharp contrast, we found[22] that the hitherto unknown *N*-acetylnorpseudotropine hydrochloride (**14**) melted at ca. 70°C and then, on continued heating, resolidified and melted again at 210°C. This high-melting product was found to be only weakly acidic, i.e. it behaved as a normal ammonium salt. We concluded that the *N*-acetyl compound had been rearranged to give the *O*-acetyl isomer. The new product was an amino ester hydrochloride, *O*-acetyl norpseudotropine hydrochloride (**16**). This acyl migration could only have occurred via a bridged intermediate (**17**), (Scheme 6). This result thus established the steric proximity of the nitrogen and the C-3 hydroxy group; pseudonortropine had the *syn* configuration and nortropine was the *anti*-stereoisomer. Since methylation

§ Although this work was subject to patent applications as early as 1942, the war delayed issuing the patents, for example Chinoin, Austrian Patent 164,549 (1949).

of nortropine gave tropine and likewise norpseudotropine gave pseudotropine without affecting the C-3 OH, the configurations of the 3-tropanols were established. This stereochemical conclusion — that these compounds were α- and β-isomers — was then generalized, upon R. S. Cahn's suggestion, to a large number of tropane alkaloids. Thus an experiment in a melting point tube led to the solution of an intriguing and important stereochemical problem. Of course, the N→O migration is not limited to a melting point tube, Nickon and Fieser subsequently reported[23] a similar rearrangement with *N*-benzoylnorpseudotropine in a solvent.



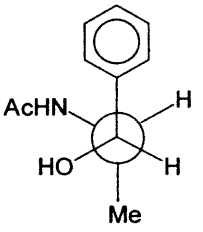
Scheme 6.

All three examples together show that the observation of the transformations of micro quantities of a compound is possible in a melting point tube. *Observation is one of the strongest weapons that the organic chemist has!*

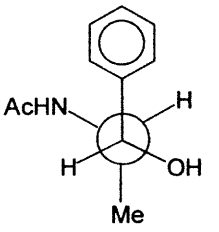
3. Critical attitude vs. hypothesis

Over many years, the author has recognized that one has to examine hypotheses critically. The dispelling of the myth of the so-called dibromodicholestanyl benzoate that survived for many years is an example where the doubt cast on a structure, the formation of which could not be explained mechanistically, was a positive experience. Another time, not much later in the author's life, was the observation of a striking difference in the behavior of norephedrine and norpseudoephedrine derivatives. In that case, no configurational assignment was needed, because that had been made earlier. However (the late) Joseph Kiss and the author found that treatment of *N*-acylephedrines and *N*-acylpseudoephedrines with alcoholic hydrogen chloride showed a drastic difference between each diastereoisomeric pair. The former failed to undergo N→O acyl migration while the pseudoephedrine derivatives (acyl=acetyl, benzoyl, carbobenzoxy) underwent fast and complete rearrangement to give the aminoester hydrochlorides[24] (Scheme 7). At that time, the hypothesis of free rotation around the C–C single bond was generally accepted; therefore the colleagues with whom this author discussed this observation of positive acyl migration in one stereoisomer and no acyl migration in the other were skeptical. They noted that such a difference sharply contradicted the conclusion presented in K. Freudenberg's monograph 'Stereochemie',[26] the major collection of important stereochemical rules formulated in the 1930s. In the chapter on ephedrine and pseudoephedrine, Freudenberg and Ebel predicted there would never be a chemical reaction whereby one could distinguish between the two because of free rotation around the C–C single bond. Applying

this hypothesis of free rotation to N→O migration, in the acyl derivatives of both ephedrine and pseudoephedrine, the hydroxyl and the acylamino groups apparently can be close together, allowing bridging between the acyl(carbonyl) carbon (followed by cleavage of the intermediate hydroxyoxazolidine into the *O*-acylamino ester hydrochloride). So there was doubt cast by my colleagues on the correctness of our observation and conclusion. However, the critics did not realize — as Freudenberg did not — that the two different aminoalcohols have bulky groups (Ph and Me) on the two neighboring carbons which lead to conformational differences (Scheme 7). The logical explanation of this stereospecificity lies in the steric repulsion between the methyl and phenyl groups. A simple space-filling model showed that in each stereoisomer, the conformation with the phenyl and methyl groups *trans*-oriented (antiparallel) must be preferred (lower energy) relative to the conformations with these groups skew-oriented. The antiparallel orientation of the phenyl and methyl groups means that in the ephedrines, hydroxyl and acylamido groups are antiparallel, inhibiting acyl migration while in pseudoephedrine (also in chloromycetine[25]) they are skew-oriented, promoting acyl migration (Scheme 7). This recognition means that the doubts we raised about the hypothesis of free rotation and the new interpretation were justified,[¶] especially in light of Barton's ingenious conformational analysis. Indeed, Barton himself used this example as support for his elegant development of conformational analysis in aliphatic compounds.[27]



N-acyl-(+)-nor-pseudo-ephedrine



N-acyl-(−)-nor-ephedrin

acyl = acetyl, benzoyl, benzyloxycarbonyl

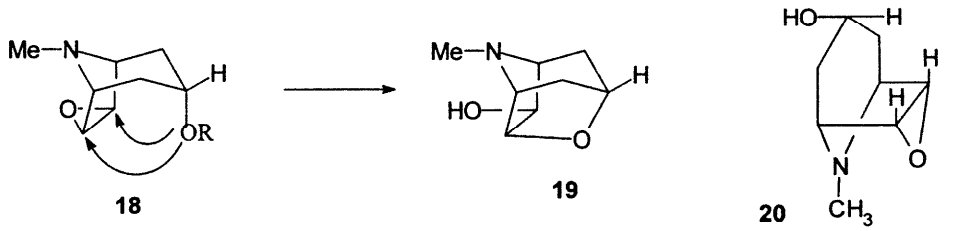
Scheme 7.

4. Prediction of reactivity based on correct modern theories

Of course, it would be a mistake not to recognize the constantly increasing power of deduction that is made possible by the assistance of physical organic chemistry's armament. For example, my most pleasant souvenir in that respect is the elucidation of the configuration of scopolamine, by

[¶] A referee criticized the stereochemical interpretation we gave stating that it ignored the Curtin–Hammett principle. Since our explanation preceded that principle by several years, we should not be accused of ignoring it. The Curtin–Hammett principle states that the relative amounts of products formed from intercoverting conformational isomers are independent of the relative amounts of the ground state conformers. The discussion above deals with the preferred conformation of two diastereomers, not conformational isomers. In the norpseudoephedrine derivative, the lowest energy conformation clearly closely models the transition state for rearrangement. In contrast, with the norephedrine derivative, rearrangement obviously cannot occur from a transition state resembling the lowest energy conformation. The skew conformations having the hydroxyl and acylamino groups gauche are clearly much higher in energy than the ground state conformer; i.e. they would model high energy transition states for rearrangement. Hence rearrangement does not occur.

reinterpreting previous experiments. This stereochemical problem was solved in three widely separated laboratories,[28] almost simultaneously by regarding the known rearrangement of scopine (**18a**), the alkamine of scopolamine (**18b**), to oscine (**19**) in terms of Ingold's electronic theory of nucleophilic substitution. Willstätter[29] correctly considered the four possible stereoisomers of scopine, but was hampered by his mentor's (A. Baeyer) strain theory, and thus assumed a planar six-membered piperidine ring for scopine (**20**). With the advent of the Sachse–Mohr theory and W. Hückel's proof of the three-dimensional, non-planar structure of cyclohexanes in *cis*- and *trans*-decalin it was obvious that this concept was not tenable, especially after the birth of conformational analysis. But the question was how to prove this configuration? In this case, deduction from known electronic and stereochemical principles helped chemists to solve the structure correctly. Meinwald, Cookson, and the present author, completely independently, discovered in 1952–1953 that the problem could be solved by making a 3D model of oscine (**19**), the product of the alkaline cleavage of scopine. This model showed that the tetrahydrofuran ring of oscine, overbridging the distance between carbons 3 and 6 of scopine, must originate from an *exo*-epoxide by a rearward nucleophilic attack of oxygen-3 from the *endo* side of the epoxide ring of scopine (Scheme 8). The stereochemistry established for scopine clearly could be extended to scopolamine. Thus, by correctly reinterpreting old findings without further experiments, in the light of modern physical organic chemistry it was possible to deduce the configuration of scopolamine on carbons 3, 6 and 7.



(a) R = H

(b) R = S(−)-tropoyl

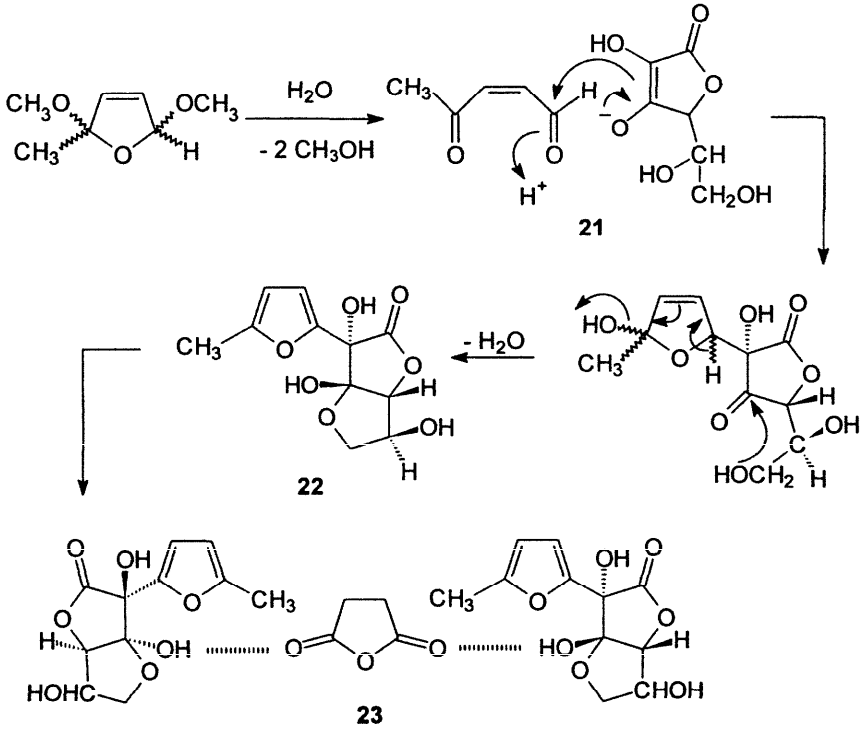
Scheme 8.

5. A renewal of L-ascorbic acid chemistry

Many years after the discovery and the synthesis of vitamin C, an unexpected observation led to a new area of the chemistry of this fascinating compound. Albert Szent-Györgyi with whom this author resumed scientific collaboration in 1965, working on retine and other topics,[30] attached great interest to the biological role of methylglyoxal. This simple compound was isolated by Szent-Györgyi from calf liver and identified by us[31] in 1978. The enzyme glyoxalase was known for a long time, but the ketoaldehyde itself had not been previously isolated from mammalian tissue. It was supposed by Albert that it played an important role in cell division. Therefore he tried to reintroduce it into rodents; unfortunately, methylglyoxal proved to be toxic. Therefore, Szent-Györgyi asked this author to detoxify it by attaching the ketoaldehyde to a carrier from which it might be detached at the site where it is needed. Our first choice was L-ascorbic acid on the basis that it might well be a carrier already used by nature. We planned to form a cyclic acetal-ketal, involving carbons 5 and 6 of ascorbic acid. After unsuccessful attempts to make an acetal under anhydrous conditions, we tried using a concentrated aqueous solution of ascorbic acid. To our surprise, when monitoring the reaction by using Szent-Györgyi's iodometric

titration of the enediol group, we found that this moiety disappeared in a short time, proving that the reducing group of ascorbic acid was consumed rapidly.

Unfortunately, many compounds were formed in this experiment and separation by HPLC and other chromatographic methods was not feasible. But this reaction intrigued us and since this mixture showed some immunopotentiating effect (Dr. R. Veltri, immunologist) it seemed interesting to study this newly discovered chemistry of ascorbic acid. Therefore, we chose to investigate the vinylogue of methylglyoxal: acetylacrolein, 4-keto-*cis*-2-pentenal (**21**), a compound easily accessible from 2-methylfuran. In aqueous solution ascorbic acid again was consumed, and after evaporation a low-melting solid formed. It was later characterized as a molecular compound with succinic anhydride.[||] A complex which was identified in the Naval Research Laboratory by Isabella Karle.[32] This study established that the new compound was 2-(5-methyl-2-furyl)-3-keto-L-gulonolactone-3,6-cyclohemiketal (**22**) and that the complex involved a unique H-bonded structure (**23**) (Scheme 9). The formation of this furan can be explained by assuming a nucleophilic addition of ascorbic acid at the aldehyde carbon of the unsaturated ketoaldehyde.

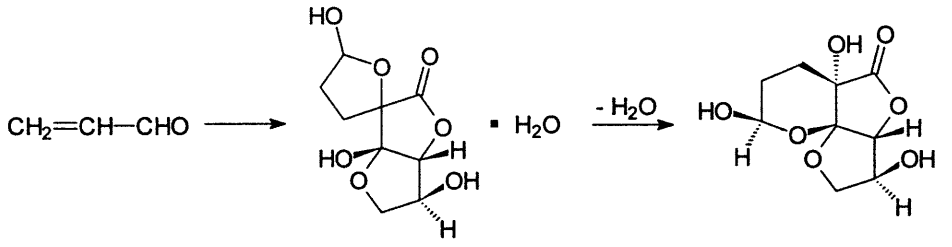


Scheme 9.

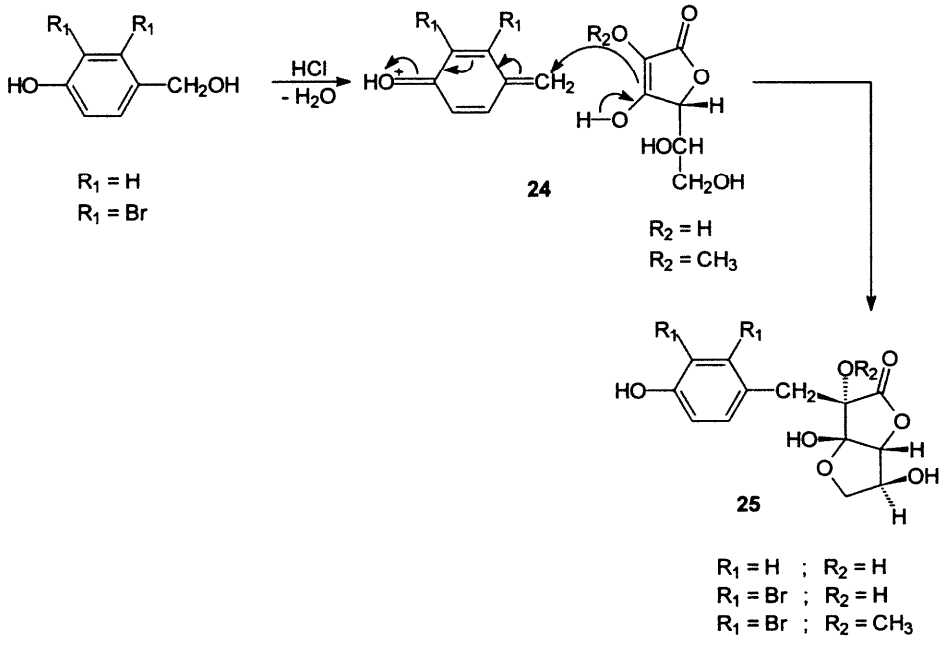
A literature search showed one observation of an alkylation of this kind: the C-2 benzylation of sodium ascorbate.[33] The formal rearrangement of the acetonide of 2-*O*-cinnamoyl-3-methyl ascorbic acid to C-2-methyl-2-*O*-cinnamoyl-3-keto-L-gulonolactone may also be considered as an analogy.[34] Later on we found[35] that ascorbic acid can undergo the Michael reaction as a donor, with a variety of α,β-unsaturated

[||] Succinic anhydride was added in order to form a succinic acid hemi-ester with one of the hydroxyls. This reaction, however, did not happen; instead a white crystalline material precipitated from the ethyl acetate solution. The NMR spectrum of this material, established that it was an addition compound of the starting materials. X-Ray crystallography by Isabella Karle and her associates showed that the crystals consisted of an H-bonded complex of furan derivative **22** with succinic anhydride; a unique structure of a hydroxyl group attached by hydrogen bonds to the carbonyl group of an anhydride **23**.

aldehydes and ketones, e.g. acrolein (Scheme 10) and methylvinyl ketone. The ingenious extension of this reaction to 4-hydroxybenzyl alcohols that, in acidic medium, react as quinone methides (**24**) (Scheme 11) led Poss and Belter[36] to the synthesis in single step of a variety of natural products (**25**): delesserine, rhodomelol, leucodrine and leudrin. The only previous synthesis of one of these compounds took more then ten steps to build up the skeleton. It is conceivable that nature made use of this type of ascorbic acid reaction for the biosynthesis of these products. Thus, the observation regarding the enediol group of ascorbic acid opened new avenues to a variety of interesting compounds.[35]



Scheme 10.



Scheme 11.

In concluding with this example of the role of observation in science, we want to emphasize how careful observation, often of seemingly minor events, can lead to many new discoveries. We hope that this article will encourage young chemists to develop their powers of observation and to follow-up on what they observe.

Acknowledgements

The author is indebted to Professor William R. Moore for his help in editing the manuscript. Thanks are due to Professor Kung Wang and Herman Odens, M.S. for their help with the formulas.

References

1. Szent-Györgyi, A. *Biochem. J.* **1928**, *22*, 1393; Svirbely, J. L.; Szent-Györgyi, A. *Nature* **1932**, *129*, 576.
2. Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441; Dr. W. R. Moore called my attention to this observation.
3. Woodward, R. B.; Ayer, W. A.; Beaton, J. M.; Bickelhaupt, F.; Bonnett, R.; Buchschacher, P.; Closs, G. L.; Dutler, H.; Hannah, J.; Hauck, F. P.; Itô, S.; Langemann, A.; Le Goff, E.; Leimgruber, W.; Lwowski, W.; Sauer, J.; Valenta, Z.; Volz, H. *J. Am. Chem. Soc.* **1960**, *82*, 3800.
4. Wasserman, H.; Lu, T.-J.; Scott, A. Ian *J. Am. Chem. Soc.* **1986**, *108*, 4237.
5. Fodor, G.; Csokán, P. *Annalen* **1938**, *535*, 284.
6. Földi, Z.; Fodor, G. *Chem. Ber.* **1941**, *74*, 589.
7. Hungarian Patent Application, 3 January 1939.
8. Fodor, G.; Szarvas, P. *Chem. Ber.* **1943**, *76*, 334.
9. Campbell, N. R.; Dodds, E. C.; Lawson, W.; Noble R. L. *The Lancet* **1939**, *II*, 312.
10. Campbell, N. R.; Dodds, E. C.; Lawson, W. *Nature* **1938**, *142*, 1121.
11. Dodds, E. C.; Lawson, W.; Goldberg, L.; Robinson, R. *Proc. R. Soc. London, B.* **1941**, *B127*, 140.
12. Carlisle, C. H.; Crowfoot, D. *J. Chem. Soc.* **1941**, 6.
13. U.S. Patent 1,350,718, 1944.
14. Obermüller, K. Z. *Physiol. Chem.* **1891**, *15*, 42.
15. Dorée, Ch.; Orange, L. *J. Chem. Soc.* **1916**, *109*, 58.
16. Petrow, V. A. *J. Chem. Soc.* **1937**, 1077.
17. Bretschneider, H.; Földi, Z.; Galinovsky, H.; Fodor, G. *Chem. Ber.* **1942**, *74*, 1451.
18. Fodor, G. *Hungarica Acta Chimica* **1947**, *1*, No. 2, 1–9.
19. Winstein, S.; Grob, C. A. *Helv. Chim. Acta* **1952**, *35*, 782.
20. Barton, D. H. R.; Miller, E. *J. Am. Chem. Soc.* **1950**, *72*, 1066.
21. Polonovski, M.; Polonovski, N. *Bull. Soc. Chim. Fr.* **1926**, *39*, 1147.
22. Fodor, G.; Nádor, K. *Nature* **1952**, *169*, 462.
23. Nickon, A.; Fieser, L. F. *J. Am. Chem. Soc.* **1953**, *74*, 5566.
24. Fodor, G.; Kiss, J. *Nature* **1949**, *163*, 287; Fodor, G.; Bruckner, V.; Kiss, J.; Óhegyi, G. *J. Org. Chem.* **1949**, *14*, 337.
25. Fodor, G.; Kiss, J.; Sallay, I. *J. Chem. Soc.* **1951**, 1858.
26. Freudenberg, K. *Stereochemie*; Deuticke: Leipzig, 1932; pp. 667–688.
27. Barton, D. H. R.; Cookson, R. C. *Quart. Revs.* **1956**, *10*, 44–75; *The Principles of Conformational Analysis*, pp. 52, 74.
28. Meinwald, J. *J. Chem. Soc.* **1953**, 713; Cookson, R. C. *Chem. Ind.* **1953**, 337; Fodor, G. *Nature* **1952**, *170*, 278.
29. Willstätter, R.; Berner, E. *Chem. Ber.* **1923**, *56*, 1079.
30. Fodor, G.; Sachetto, J.-P.; Szent-Györgyi, A.; Együd, L. *Proc. Natl. Acad. Sci. USA* **1967**, *57*, 1644.
31. Fodor, G.; Mujumdar, R.; Szent-Györgyi, A. *Proc. Natl. Acad. Sci. USA* **1978**, *75*, 4317.
32. Fodor, K.; Sussangkarn, K.; Mathelier, H.; Arnold, R.; Karle, I.; George, C. *J. Org. Chem.* **1984**, *49*, 5064.
33. Jackson, K. G.; Jones, J. K. N. *Can. J. Chem.* **1965**, *43*, 450.
34. Brimacombe, J. S.; Murray, Z. W.; Zhur-ul Hague, *Carbohydr. Res.* **1975**, *45*, 45.
35. Fodor, G.; Sussangkarn, K. New chemistry of vitamin C. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed. Elsevier: Amsterdam, 1989; vol. 4, pp. 699–729.
36. Poss, A. J.; Belter, R. K. *J. Org. Chem.* **1989**, *53*, 1535.
37. Bachmann, W. E.; Cole, W.; Wilds, A. L. *J. Am. Chem. Soc.* **1940**, *62*, 824.