THE BECKMAN CENTER FOR THE HISTORY OF CHEMISTRY

LEO H. STERNBACH

Transcript of an Interview
Conducted by

Tonja Koeppel

at

Hoffmann-La Roche Inc.
Nutley, New Jersey

on

12 March 1986

THE BECKMAN CENTER FOR THE HISTORY OF CHEMISTRY
Oral History Program

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LEO H. STERNBACH

1908 Born in Abbazia, Austria on 7 May

Education

University of Cracow
1929 M. Pharmacy
1931 Ph.D., organic chemistry
1931-1937 Research Assistant with Professor K. Dziewonski

1937-1940 Research Fellow with Professor L. Ruzicka, Eidgenössiche Technische Hochschule, Zürich

Professional Experience

1940-1941 Research Chemist, Hoffmann-La Roche, Basel, Switzerland

Hoffmann-La Roche, Nutley, New Jersey
1941-1959 Group Chief
1959-1965 Senior Group Chief
1965-1967 Section Chief
1966-1973 Director of Medicinal Chemistry
1973- Consultant

Honors

1971 Honorary Dr. of Technical Sciences, Technical University, Vienna, Austria
1977 Outstanding Naturalized Citizen Award, Newark Chapter, Unico National
1978 Medicinal Chemistry Award, American Chemical Society, Division of Medicinal Chemistry
1979 Cecil Brown Lectureship, American Chemical Society, North Jersey Section
1979 Award for Creative Invention, American Chemical Society
1979 Chemical Pioneer Award, American Institute of Chemists
1982 John Scott Medal Award, Board of Directors of City Trusts, Philadelphia, Pennsylvania
1984 Charles W. Hartman Memorial Lecture, University of Mississippi
1984 Honorary Doctor of Science, Centenary College, Hackettstown, New Jersey
1984 Carl-Mannich-Medal, German Pharmaceutical Society
1986 Honorary Dr. phil. nat. h.c., Johann Wolfgang Goethe-Universtät, Frankfurt am Main

ABSTRACT

Leo H. Sternbach begins the interview with a discussion of his family and childhood in Austria and Poland. He describes his early education during the First World War as well as his experiences working in his father's pharmacy. After receiving a degree in pharmacy from Jagiellonian University in Cracow, he enrolled in a Ph.D. program in organic chemistry. As a result of intensifying anti-Semitism, he left Poland and went to Vienna, where he worked with Pauli and Fränkel, and then to Zürich to work with Ruzicka at the Swiss Federal Institute. After beginning work with Hoffmann-La Roche in Basel and marrying Herta Kreuzer, increasing pressure to leave Switzerland compelled him to emigrate to the United States, where he continued work with the company in Nutley, New Jersey and began a search for new tranquilizers. Sternbach recalls that he was instructed to terminate his study of benzodiazepines but continued the research unofficially, which led to his significant discoveries of Librium, Valium, and other related drugs. He concludes the interview with a brief summary of his accomplishments and his views on the present state of pharmaceutical research.

INTERVIEWER

Dr. Tonja A. Koeppel received a master's degree in chemistry from the Swiss Federal Institute of Technology in 1944. Since then she has written about chemistry, done research, and taught college chemistry. Dr. Koeppel is also a historian of chemistry. In 1973 she earned a Ph.D. degree in the history and sociology of science from the University of Pennsylvania. She is especially interested in the development of organic chemistry in the nineteenth and early twentieth centuries.

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INTERVIEWER: Tonja Koeppel

LOCATION: Nutley, New Jersey

DATE: 12 March 1986

KOEPPEL: Dr. Sternbach, I would like to ask you a few questions about your early childhood. I know that you were born on May 7, 1908 in Abbazia which was then Austria, and that your parents were originally not from Austria.

STERNBACH: My parents were Austrians. You know, Abbazia belonged to Austria at that time. My father was from Przemysl, a town in the eastern Polish-speaking part of the Austrian province of Galicia. My mother was from Hungary, and they met in Abbazia where my father had a pharmacy.

KOEPPEL: I see. This was considered to be the Austrian-Hungarian Empire? You were really Austrian in this case.

STERNBACH: Yes, I was Austrian.

KOEPPEL: What language did you speak?

STERNBACH: At home we spoke German, because my father didn't know any Hungarian and my mother didn't know any Polish at that time. So the "lingua franca" was German.

KOEPPEL: Did you have any brothers and sisters?

STERNBACH: At that time I had a brother who was three years younger than I. He died of scarlet fever after we moved to Poland.

KOEPPEL: Was he your only brother?

STERNBACH: Yes. He was my only brother.

KOEPPEL: So you were then left as an only child.

STERNBACH: Yes. My brother died when I was eighteen years old.

KOEPPEL: I see. What was your father's name?

STERNBACH: Michael Sternbach.

KOEPPEL: What was your mother's maiden name?

STERNBACH: Cohn. The given name was Piroska. It's a Hungarian name.

KOEPPEL: Your father was a pharmacist. Where did he study?

STERNBACH: I think he studied in Lwów, Lemberg, and finished his pharmacy studies there. After the First World War he was employed in a pharmacy in Cracow. He moved to Abbazia before I was born. It must have been around 1903. He rented a pharmacy there. He did very well as long as Abbazia was Austrian since Abbazia was the only seashore resort in the Austrian Empire.

KOEPPEL: Did your mother have a university education?

STERNBACH: No. My mother attended a "höhere Töchterschule," a high school for girls.

KOEPPEL: Was she a housewife?

STERNBACH: Yes, she was a housewife.

KOEPPEL: Do you have any memories of the pharmacy?

STERNBACH: Yes.

KOEPPEL: I remember when I was young pharmacies always had such a wonderful smell.

STERNBACH: Yes, they did. I helped my father sometimes. During the First World War my father couldn't employ anybody since business was very bad, so he was alone there. Very often we had supper in the pharmacy, because he kept it open until eight and even later. Sometimes my mother then made some eggs or something

similar for supper. Sometimes I would watch the pharmacy while my father had a fifteen-minute nap after lunch and take care of people who came in. I asked them in German or Croat to please wait a minute or so.

KOEPPEL: That must have been fascinating, because children like to sell.

STERNBACH: Well, I couldn't sell at that time. I was only seven to ten years old.

KOEPPEL: But it must have influenced your career choice, because I see that you later studied pharmacy.

STERNBACH: Yes. I studied pharmacy because my father had the pharmacy in Cracow, Poland. And at that time, sons and daughters of pharmacists had preference to be accepted at the University. There were only thirty places in the pharmacy program. So I was accepted as a son of a pharmacist.

KOEPPEL: I would like to go back to your grade school, because you started your schooling at such a crucial time, in 1914?

STERNBACH: Yes, it was in 1914. This was a German-speaking school. I mean, this was in Austria, so it was German. Everything was in German, and it went on until I finished the elementary school. The elementary school was four years at that time and then we had eight years of "higher education." For four years I did it in German. Then the Italians occupied Abbazia, after the First World War was over. That was in 1918.

KOEPPEL: You were not actually involved in the war. The war did not affect your early schooling, or did it?

STERNBACH: No. We heard some fighting on the Isonzo River, some artillery shooting, and one bomb fell even in the woods of Abbazia, which made a hole just about two meters in diameter. This was a bomb dropped by an Italian flyer.

KOEPPEL: Was your father drafted?

STERNBACH: No, he wasn't. He volunteered, but they didn't take him. I think it was because he was a pharmacist.

KOEPPEL: They needed him.

STERNBACH: Yes, and he was probably also overage.

KOEPPEL: You must have been a good student in grade school.

STERNBACH: No, I wasn't very good. In some subjects I was good, such as mathematics.

KOEPPEL: Mathematics and science?

STERNBACH: Yes, I was good in physics.

KOEPPEL: But in grade school you really didn't have this specialized training, did you?

STERNBACH: What do you mean by grade school?

KOEPPEL: Primary school.

STERNBACH: The elementary school. There we had just reading, writing, and mathematics. I don't know whether we had a little bit of science. In any case, certainly not as much as here. Then I started the Gymnasium at Abbazia. It was a German Gymnasium, but as soon as the Italians came, it was closed, and only Italian schools existed.

KOEPPEL: Did they force you to change the language and learn Italian?

STERNBACH: No. At that time we started to learn Italian. I knew it fairly well, but was not sufficiently fluent to continue my studies in Italian. So we had private lessons (in German). I learned privately with two or three others. We brought a high school professor from Austria to Abbazia, and he taught us in German. I took yearly exams in Villach in Carynthia (Kärnten). I think we did that for two years and then we had another private teacher. But this didn't work very well. We just barely passed the exams. Later on, when I was thirteen and in the fourth grade of high school, I was brought to Villach and went to the high school there. I had room and board with a Mrs. Scheucher.

KOEPPEL: How long did you attend the Gymnasium?

STERNBACH: For eight years.

KOEPPEL: For eight years. That was from 1914 to 1922.

STERNBACH: No. I started elementary in 1914. It was from 1918 to 1926.

KOEPPEL: You must have demonstrated special talents in high school.

STERNBACH: Not particularly. In the first or second year of high school I knew that I wanted to be a chemist.

KOEPPEL: I see. You went into chemistry through pharmacy.

STERNBACH: Yes, through pharmacy. I knew that my father wanted me to be a pharmacist and take over the pharmacy.

KOEPPEL: And you wanted to be a chemist?

STERNBACH: Yes.

KOEPPEL: Did you have chemistry in high school?

STERNBACH: Very little. In those days you had one hour of chemistry a week for one or two years. It was a very limited program.

KOEPPEL: Did you have a laboratory?

STERNBACH: No. There wasn't any laboratory.

KOEPPEL: But you were good in mathematics.

STERNBACH: I was good in mathematics and I had my own laboratory, which was my window sill. I ruined several window sills, and even when I was in Villach with Mrs. Scheucher, I destroyed her window sill.

KOEPPEL: In her home in Villach?

STERNBACH: Yes, and my parents then had to pay for repair or replacement of the window sill.

KOEPPEL: No wonder your father didn't want you to study chemistry. [laughter] Now, at age sixteen, which would be in 1924, you went back to Poland. What was your educational status at that point?

STERNBACH: Actually, it was a little bit earlier. We went to Poland when I was fifteen, which would have been 1923. My parents moved back to Poland, and I moved with them. Let me see, how was it? When I was in fifth grade, then I was five plus ten is fifteen. In 1923 my father knew that he would get a pharmacy concession in Poland in 1923 or 1924. Then he started to prepare for that. Since I had to be away from home anyway, he sent me to the German-speaking Gymnasium in Bielitz (Bielsko) in Poland.

KOEPPEL: That was a German-speaking school?

STERNBACH: Yes, it was German-speaking. They had two full German-speaking Gymnasia in Poland. One was in Bielsko and the other in Stanislawów because of a German enclave.

KOEPPEL: And so you finished your Gymnasium in Poland, in German.

STERNBACH: I finished in German, but I had to learn Polish very intensively. That meant an hour of Polish everyday. I had to pick up everything I hadn't had for three years, and then go on from there.

KOEPPEL: You were really bilingual by that time.

STERNBACH: Well, the Poles didn't think so. It is a very difficult language to learn. I had to learn it for the whole time, and even when I was a university student my Polish wasn't perfect. But I also knew some Hungarian. My mother always spoke Hungarian with me.

KOEPPEL: Was the university which you now entered the University of Cracow?

STERNBACH: Yes, the Jagiellonian University in Cracow.

KOEPPEL: There the instruction was in Polish?

STERNBACH: Yes, everything was in Polish.

KOEPPEL: You were enrolled in the pharmacy curriculum.

STERNBACH: Yes, it was attached to the department of philosophy. The pharmacy curriculum took three years, and you got the degree of a master of pharmacy.

KOEPPEL: You got that degree in 1929. You took also chemistry courses. Were you allowed to take additional chemistry courses?

STERNBACH: No. In the pharmacy program, our time was completely filled out...

KOEPPEL: ...with pharmacy. But you did have chemistry.

STERNBACH: I had quite a lot of chemistry.

KOEPPEL: What kind of chemistry?

STERNBACH: Inorganic and organic chemistry, not medicinal chemistry specifically.

KOEPPEL: And no biochemistry.

STERNBACH: No biochemistry. We also had basic botany and we learned about plants, about drugs, about medicinal plants that contain drugs, and so on.

KOEPPEL: Pharmacology?

STERNBACH: Not pharmacology but pharmacognosy, which means to recognize plants. We had nothing to do with animal experiments.

KOEPPEL: Were there any professors that you found especially stimulating, who influenced you or confirmed you in your intention to study chemistry?

STERNBACH: Well, yes. Later on I studied, with Professor [K.] Dziewonski. He was the professor of organic chemistry. I applied to work on the Ph.D. with him, and he accepted me. I finished the Ph.D. with him and stayed on as an assistant.

KOEPPEL: So you went from the school of pharmacy to a graduate program in chemistry?

STERNBACH: Yes, in organic chemistry. I had really to add very little to my curriculum and mostly just worked on my doctor's thesis. I studied a little bit of crystallography, and other minor subjects which we did not have as pharmacists.

KOEPPEL: And your doctoral thesis was concerned with indigo dyes.

STERNBACH: Yes, it was with thioindigo dyes.

KOEPPEL: You worked a lot with aromatic amines.

STERNBACH: Yes, with napthylamine and later on I worked with chloroaniline and similar compounds. But the first publication with Professer Dziewonski was on napthothioindigo (1).

KOEPPEL: But it did get you into heterocyclic compounds which proved to be important for you later.

STERNBACH: Yes, very much so.

KOEPPEL: Was there anything in the dye field that came out of this work?

STERNBACH: Well, it was a synthesis of napthothioindigo, but it was not of great value. It was a reddish-brown dye, but did not have any practical value.

KOEPPEL: I've read that you had a special talent for crystallization.

STERNBACH: Yes, I love to crystallize. I always did. I loved to have crystalline compounds, and in Switzerland some people said that I can even crystallize Swiss cheese. [laughter]

KOEPPEL: Were there any colleagues that you met again later? I remember that we had a lot of Polish people at the Swiss Federal Institute of Technology [ETH].

STERNBACH: Yes. There were many Poles in Switzerland. A regiment of the Polish army was pushed over the border and then interned in Switzerland. They were quite free there, and they even had a university, a "Hochschule" in Winterthur.

KOEPPEL: Yes, I remember.

STERNBACH: I was lecturing there too, in organic chemistry.

KOEPPEL: But that was later. While you were still in Poland, were there any people you met again in Zürich?

STERNBACH: Yes. There was my friend Hellerbach, who later onwas in the Polish army and ended up in Switzerland.

KOEPPEL: Yes. I knew Hellerbach.

STERNBACH: Oh, you knew him? Oh, he was a very good friend of mine.

KOEPPEL: What was his first name?

STERNBACH: Josef.

KOEPPEL: Josef Hellerbach. He was an officer in the Polish army, and was interned.

STERNBACH: Yes, he was interned.

KOEPPEL: He worked in the same lab as I did.

STERNBACH: Oh, really? At the Poly [ETH], in Ruzicka's place?

KOEPPEL: Yes. To go back to Cracow, I would be interested to know how the labs were organized at the University.

STERNBACH: In Cracow, we had labs with laboratory benches, constructed in such a way that about three or four people worked on one side of the bench, three or four people on the other, and there were maybe four or six such benches. Once we had a fire there. I mean a very bad fire. A girl was distilling...

KOEPPEL: A girl?

STERNBACH: Yes, a pharmacy student. She was distilling benzene on the steam bath. There was a flame under the steam bath and the benzene caught fire. And it was even more horrible because her clothes caught fire. She had a celluloid comb [in her hair] which caught fire and fell into her clothes. It burned a hole in her back. She died a few days later.

KOEPPEL: She died from the accident?

STERNBACH: Yes, she died.

KOEPPEL: That must have been a traumatic experience.

STERNBACH: Yes, it was terrible. Then they removed in each row one of the four laboratory working places. Then there were three. They cut off one in order to widen the passage and have a better chance to escape or to move around.

KOEPPEL: So it was a relatively small laboratory.

STERNBACH: Well, it could have held maybe fifty to sixty students.

KOEPPEL: Oh, that many.

STERNBACH: Yes.

KOEPPEL: Did you have teaching assistants? Was it the same system as we have here?

STERNBACH: Yes. We had teaching assistants there. Later on I became a teaching assistant in the organic chemistry course for pharmacists.

KOEPPEL: You then stayed on as a research assistant to Professor Dziewonski?

STERNBACH: Yes.

KOEPPEL: I noticed that you already had some publicationswhile you were still in Poland (1), (2) [and seven additional papers].

STERNBACH: Yes, as a postdoctoral student.

KOEPPEL: As a postdoctoral student you published on aromatic amines and on pyrene and...

STERNBACH: ...and on the Friedel-Crafts reactions with these aromatic amines.

KOEPPEL: Do you remember the journal?

STERNBACH: Roczniki Chemii. That's a Polish journal. It could be translated as "Yearly Reports in Chemistry," or something like that. Also in the Bulletin of the Polish Academy of Sciences.

KOEPPEL: In 1937 you went to Zürich. Was that because war was imminent?

STERNBACH: No, it was due to the fact that I didn't have any chance at the University because I was Jewish.

KOEPPEL: Really?

STERNBACH: Even Professor Dziewonski told me so. Yes, anti-Semitism is one of the very strong feelings of the Poles.

KOEPPEL: I see.

STERNBACH: Dziewonski was very nice in that respect. He told me, "Look, you have no chances here. There is a grant coming up by the Eeliks Wislicki Foundation." Wislicki was Jewish too, and he was the owner or director of one of the biggest viscose plants. Viscose is nitrocellulose. Professor Dziewonski said, "This grant is coming up and I, Dziewonski, am on the committee. I will support your application if you apply." And so I did that. He told me, "In the outside world you will do much better than you can do here." So I applied for it and really got the grant.

KOEPPEL: And the grant allowed you to study at the ETH?

STERNBACH: No, wherever I wanted, but it was meant for colloidal chemistry. I wrote to Professor Pauli (the father of the famous Wolfgang Pauli, of the Pauli Principle who then was in Zürich).

KOEPPEL: That was the father. What was his position?

STERNBACH: Wolfgang Pauli was professor of colloidal chemistry in Vienna.

KOEPPEL: Oh, I see. I see, in Vienna, not the Swiss Federal Institute.

STERNBACH: Yes. He was in Vienna. I applied to go there and was accepted. I came to Vienna and hoped that I could possibly work half-days in colloidal chemistry and half-days in organic chemistry, which interested me. As soon as I arrived in Vienna I discussed with Professor Pauli what my task would be. I had to do conductivity determinations of very dilute agar solutions and similar measurements. It really didn't interest me very much, but that was my work and my chance to get out of Poland.

KOEPPEL: So, you actually went to Vienna. I see a paper here on comparative electrochemical studies, and I was wondering where that came from (3).

STERNBACH: Yes, that was in Vienna with Professor Pauli.

[END OF TAPE, SIDE 1]

KOEPPEL: We were talking about your work in Vienna with Professor Pauli. Can you tell us a little bit more about it?

STERNBACH: Yes. I did this work with Professor Pauli, but I hoped I could arrange it so that I would work half-days in colloidal chemistry and half-days in organic chemistry, which is what I really was interested in. So I went to the well-known Professor [Ernst] Späth who at that time was professor of organic chemistry in Vienna. I went to him and asked, "Wouldn't it be possible for me to work half-days in your laboratory?" But Professor Späth said, "No, that's not possible."

First of all, he could not take me on the spot, and second, he didn't have the space. In addition, he would not take anybody for half-days only. Therefore I went to Professor [Sigmund] Fränkel. Fränkel had written a book called Die Arzneimittel Synthese (4). I can show it to you. It's a rather noncritical compilation of everything that was known at that time about the correlation between the structure and biological activity of drugs. So I went to him and he gave me a place in his laboratory that was on the Währingerstrasse. Do you know Vienna?

KOEPPEL: No, not really.

STERNBACH: It was on the Währingerstrasse, one of the big traffic arteries. And there, on the second floor, he had a laboratory. As help he had an old lady, or rather an old cleaning woman who cleaned our equipment and also cleaned the floors and everything. But, there wasn't any chemical help. She wasn't a chemist. The laboratory was miserably heated and it was therefore quite cold. I think it was the beginning of March of 1937. So I was there and was trying to work there.

He gave me a project which a former co-worker of his had started. He was working on the synthesis of quinine or the isolation of various alkaloids related to quinine, and there were many dirty mother liquors, in various containers. He said, "Well, see if you can crystallize and purify these products." "Da ist mir die Lust vergangen." [I lost my enthusiasm.]

KOEPPEL: Were you successful?

STERNBACH: Well, no. The whole thing was so disgusting. It was a project which was abandoned in the middle, with many nondescript or very ill-defined samples. So I decided I would have to terminate my association with Professor Fränkel and invent an excuse. I told Professor Fränkel, "The Foundation doesn't let me work in two places simultaneously, and I therefore have to stop my work with you." I thought I would work very intensively at Pauli's and then go for the second half of my grant year to Professor Ruzicka in Zürich. It was about that time that I had heard a lecture of Professor Ruzicka in which he described the first degradation of cholesterol to estrone-like compounds. I was very impressed!

KOEPPEL: In Vienna?

STERNBACH: Yes, in Vienna. I was very impressed when I heard him. So I wrote to Professor Ruzicka and he agreed to take me.

KOEPPEL: You hadn't approached him then [in Vienna]?

STERNBACH: No, no. Not then.

KOEPPEL: Was Professor Fränkel associated with the University?

STERNBACH: No. He was a "Ausserordentlicher Professor," a scientist working on his own, not connected with a University, not salaried. He was paid by a Foundation.

KOEPPEL: I see. So you were accepted at the ETH?

STERNBACH: Yes, I was accepted at the ETH. I started October 1 in 1937.

KOEPPEL: This was a position as a research fellow.

STERNBACH: Yes, it was as a research fellow, as a postdoctoral fellow as you would say here. They accepted me as a postdoctoral research fellow and gave me a nice working place. There was a Dr. [Moses W.] Goldberg who later joined Roche. He greeted me and he acquainted me with everything that was to be done there. He was very nice to me.

KOEPPEL: There was a whole group of promising young scientists who later emigrated. Was George Rosenkranz there?

STERNBACH: Rosenkranz was there at the same time. He started his Ph.D. thesis in the same laboratory.

KOEPPEL: Who else?

STERNBACH: Who else? Klaus Hoffman was there. He is now in Pittsburgh. He was later the assistant in charge of that lab. Goldberg was Ruzicka's private assistant and Klaus Hoffman was "Saal" assistant. Then there was Cyril Grob, who is now

professor in Basel. He was still studying and was not yet working on his Ph.D. thesis. And who else was there? There was A. Marxer who is now with Ciba in Switzerland. It was quite a good crop.

KOEPPEL: Didn't they leave for the United States at the beginning of the war?

STERNBACH: Yes, the non-Swiss left. Rosenkranz left, and so did Kaufmann, a Hungarian who is now in Mexico. I saw him just a few years ago in Zürich. (He died in 1987.)

KOEPPEL: Isn't Rosenkranz now in California?

STERNBACH: I don't know exactly. He's a very good bridge player, and has his own system. It's called Romex, from Rosenkranz and Mexico.

KOEPPEL: Oh, really? Wasn't his wife kidnapped in Washington?

STERNBACH: Yes, she was kidnapped and then freed. The ransom was also recovered.

KOEPPEL: The ransom was recovered?

STERNBACH: Yes. She was kidnaped by a bridge player.

KOEPPEL: By a bridge player?

STERNBACH: Yes, by a bridge player. He was not very good at kidnapping.

KOEPPEL: In Zürich you worked on terpenes and diterpenes.

STERNBACH: Yes, I worked on diterpenes with Professor Ruzicka. I worked on two resin acids, abietic acid and later on dextropimaric acid.

KOEPPEL: Ruzicka got the Nobel Prize when you were there in 1939.

STERNBACH: Yes, he got the Nobel Prize at that time, the year after [Paul] Karrer got it. They didn't like it that Karrer had it before him. But then the year after that Ruzicka got it.

KOEPPEL: You must have been celebrating.

STERNBACH: Oh, yes. He invited us all into a small excellent restaurant in the Niederdorf in Zürich. Do you know Zürich?

KOEPPEL: Yes, of course.

STERNBACH: I forgot the name of the restaurant. He also invited the whole group for a skiing trip to Unterwasser.

KOEPPEL: Really. That was nice.

STERNBACH: At that time the aide to Professor Ruzicka was Frau [Gertrud] Acklin. She was his secretary. She also made methyl group determinations for the chemistry department.

KOEPPEL: Wasn't she a chemist?

STERNBACH: No, she was his secretary, but not a chemist.

KOEPPEL: But she knew a lot about chemistry.

STERNBACH: Yes. [Max] Furter was there too at that time. Furter was the microanalyst who later joined Roche and became "Generaldirector" after a few years.

KOEPPEL: In the United States?

STERNBACH: No, in Basel.

KOEPPEL: So you really met a lot of interesting people in Zürich.

STERNBACH: Yes.

KOEPPEL: You also published a paper with Wolfgang Pauli (5), the father.

STERNBACH: Yes, the Viennese Wolfgang Pauli.

KOEPPEL: I see. So that was the father of the famous physicist Wolfgang Pauli. You started publishing in Helvetica Chimica Acta with Ruzicka (6).

STERNBACH: Yes, that was with Professor Ruzicka on abietic acid and dextropimaric acid.

KOEPPEL: You also met your future wife in Zürich. Would you tell us a little bit about her?

STERNBACH: Yes. I lived at 87 Universitätstrasse with a Mrs. Kreuzer. She rented a room to me and I lived there. And it was there that I met her daughter, Herta Kreuzer, whom I later married.

KOEPPEL: Was Mrs. Kreuzer Swiss or was she German?

STERNBACH: She was very Swiss. She was a Diem from Appenzell.

KOEPPEL: Oh, I see.

STERNBACH: Kreuzer was her married name.

KOEPPEL: How did you like the life in Zürich compared to the life outside of Switzerland after the war started?

STERNBACH: I stayed in Switzerland till 1941, and I liked it very much. I loved the mountains.

KOEPPEL: Did you ski?

STERNBACH: Yes, I skied then. In summer I made many excursions. Every weekend I was somewhere.

KOEPPEL: Did you go to the mountains?

STERNBACH: Yes. The Urirotstock and other mountains like that.

KOEPPEL: What about your personal relationship with Ruzicka? Did you know him very well?

STERNBACH: I knew him fairly well. He invited us off and on to something. I know a few times I didn't go. He invited us to ice hockey games and occasions like that. And a few times I couldn't go because I just had planned an excursion into the mountains. He was very nice to his students.

KOEPPEL: You mean, to his assistants?

STERNBACH: And to his co-workers.

KOEPPEL: Right. He didn't really know his other students. He had almost no contact with undergraduate students.

STERNBACH: I only knew about his relationship to his doctoral students and to his assistants.

KOEPPEL: So, it was a warm and personal relationship?

STERNBACH: Yes.

KOEPPEL: He seemed so remote to the younger students.

STERNBACH: I don't know how it was with the other students. He was a Yugoslav originally. He was very proud that he was asked to work with the Swiss "Luftschutz." He even had some laboratory space reserved for "Luftschutz" chemists where he would be able to analyze the gases or anything else that might be dropped on Switzerland. He also had a "Luftschutz" uniform, and two "Luftschutz" people under his command.

KOEPPEL: Oh, really?

STERNBACH: Yes.

KOEPPEL: He was quite demanding, wasn't he? His standards were high.

STERNBACH: Yes, they were very high. I remember one of our American colleagues. He wasn't there at the time we were supposed to be there, and Professor Ruzicka came around and made a big question mark with chalk on his bench. It was his way of just asking, "Where are you?"

KOEPPEL: Then you moved to Basel. Why did you leave the ETH?

STERNBACH: It was on my own initiative. I was really encouraged by Dr. Goldberg who said, "Look, the times are difficult. It will be very hard for Switzerland to house so many foreigners and it will be better for you if you are in industry."

At that time, Furter was already with Hoffmann-La Roche. He had called up Goldberg and told him that they needed some chemists there. Ruzicka proposed me. [A.] Grüssner joined La Roche at the same time, which was in the middle of 1940, May or June. He had worked with Reichstein on vitamin C.

KOEPPEL: Did you work on vitamin C?

STERNBACH: No, I didn't.

KOEPPEL: But you knew Tadeus Reichstein.

STERNBACH: Yes, I knew Reichstein, but just from visiting his co-workers. I had a friend working with Reichstein and so I knew him from that.

KOEPPEL: You stayed in Basel only one year.

STERNBACH: Yes.

KOEPPEL: You got married a year later, in February of 1941?

STERNBACH: Yes. It was just shortly before we left for the States.

KOEPPEL: Did your fiancée work in Basel?

STERNBACH: No, she was in Zürich and I went there usually over the weekends.

KOEPPEL: Then you got married and moved to the United States in the middle of the war. Did you come by boat?

STERNBACH: Yes, we came by boat. It was quite difficult.

KOEPPEL: Was it dangerous?

STERNBACH: It could have been dangerous because of the German U-boats. You see, according to the then existing laws my wife became Polish after she married me, and lost her Swiss citizenship. She was "ausgebürgert" and became a "tolerierte Ausländerin" at that time because the Swiss were very concerned about the many foreigners living in their country. Well, she could still work in the office where she was working, but then she got a letter declaring her a "tolerierte Ausländerin," and "we would appreciate if you would leave the country as soon as possible."

KOEPPEL: I don't believe that!

STERNBACH: Yes. "Das Schiff is voll" [the boat is full]. Hoffmann-La Roche in Switzerland was also aware of this situation and was aware that it was very difficult to keep foreigners. They had to renew my working permit every half-year with various excuses stating, for instance, that there was nobody in Switzerland who could do the work I could do. They planned to transfer me and many others in the same situation to the States. Grüssner, who was Hungarian, was also one, but he couldn't make it because his quota number would have come up only in fourteen years! (At that time the U.S. had a quota system, which very strictly regulated the number of foreigners immigrating.)

My quota was dependent on the nationality of my birthplace, after the Versailles Treaty. After the Versailles Treaty Abbazia was Italian and I came under the Italian quota.

KOEPPEL: That wasn't so full?

STERNBACH: No. The Italian quota was very good.

KOEPPEL: I'm surprised, because so many Italians emigrated to the United States.

STERNBACH: I think because of that the quota was good. It was based on how many people had entered the country within a certain time, but I don't know how it was determined exactly. But, the Italian quota was very good and the Hungarian quota was miserable. The Polish would have been miserable too.

KOEPPEL: So you were lucky you were able to come.

STERNBACH: Yes. There was no difficulty.

KOEPPEL: You don't remember the name of the boat?

STERNBACH: Yes, I do. It was the Serpa Pinto. I think it still exists. It's a small Portuguese boat. I think "serpa pinto" means small snake.

KOEPPEL: Did you land in New York?

STERNBACH: Yes, in Jersey City. They were expecting us. There was Dr. Furter and Dr. [W.] Wenner. I don't know whether you knew him. He was with Roche at that time. He was a German, but was living in Switzerland. That was also one of the reasons why he was brought over. Also, there was Dr. [John A.] Aeschlimann. I don't know whether you knew him. He was a chemist. Despite his name, he was British, because I think his parents had moved to England. He barely spoke high German. He spoke Swiss-German and English. He was married to a "ck, dt" Burckhardt.

KOEPPEL: Oh, I see. That was an aristocratic Basel family. So you came directly to Nutley.

STERNBACH: Yes. We first lived in an inn in Montclair for two weeks. Then we rented a house which was furnished and which we could afford at that time. It was really half a house, because the upper floor was occupied by other people. We could rent it for sixty dollars a month.

KOEPPEL: Times have changed.

STERNBACH: It was quite good, because my salary at that time was eighty dollars a week.

KOEPPEL: What was your position?

STERNBACH: I was a Senior Chemist, which was the lowest level of the Ph.D.s. At that time only two levels existed for Ph.D.s--the senior chemist and group chief.

KOEPPEL: Then you got settled and I would assume you made friends mainly with the Hoffmann-La Roche people.

STERNBACH: Yes, with the Hoffmann-La Roche people and mainly with the ones who were transferred at that time, because the research department was very small then. It was enlarged by the people who were brought in at that time. Max Hoffer was one of them. He's the person who invented Gantrisin. Max Hoffer was from Czechoslovakia and he was half-Jewish. Therefore he was also in need of moving out. Dr. [Werner] Lindenmaier was a plant chemist, and his wife was a Russian Jew. So they were brought here too. She's still alive. He died a few years ago. Also Dr. Goldberg died. Dr. Goldberg was brought over too. He was hired in Basel by Dr. [Emil] Barell. He came here as a group chief. At first he was meant to be a research director, but it didn't come to that. He was a group chief.

KOEPPEL: Well, we should really talk a little bit about your work now that we have come that far.

STERNBACH: Yes. When I started here, I worked on a project I had started already in Basel. It was the synthesis of riboflavin (vitamin B_2), which was split up into several steps. I was working on one step of the riboflavin synthesis, which concerned the epimerization of arabonolactone, arabonic acid to ribonic acid. I made some improvements, and it started to look better and better.

When I was brought here, the research director was Dr. Heinz M. Wüest. I didn't like him very much, and we didn't get along very well. For a while he remained as research director, but then Dr. Goldberg came over at the end of 1940 (by plane already, by Clipper) and I was assigned to his group. Dr. Goldberg got a group of people working for him.

KOEPPEL: Were you still working mainly on vitamins?

STERNBACH: No. When I worked under Dr. Wüest, he was interested in arsenicals since Marpharsen became very well known at that time. It was used in cases in which Salvarsan was used before, particularly in syphilis, as a fairly toxic but easily dosable arsenic preparation. I worked on that while I was working for Dr. Wüest. Then I was transferred to Dr. Goldberg, and we started to work on the synthesis of biotin.

KOEPPEL: Biotin was your first big achievement. Was it the technical synthesis of biotin?

STERNBACH: Yes, the technical synthesis of biotin. It was at one time called vitamin H. H for "Haut" [skin].

KOEPPEL: I see. The structure was elucidated by [Vincent] du Vigneaud.

STERNBACH: Yes.

KOEPPEL: That was in 1942. There was a lab synthesis by [S. A.] Harris.

STERNBACH: Yes, there was. Harris was with Merck. They had a synthesis, but it was completely impractical. So we developed a completely different synthesis which decreased the price. I think at that time if you would have extrapolated, a kilo would have cost seven hundred thousand dollars, and we improved the synthesis so much that we could sell it for ten thousand dollars a kilo.

KOEPPEL: That's still a lot of money.

STERNBACH: Yes, it's still very expensive. I think biotin is still in that range.

KOEPPEL: Was it actually biotinol?

STERNBACH: No. Biotin is an acid and biotinol is the alcohol obtained by reduction of that acid.

KOEPPEL: But you were also the one who developed the synthesis of biotinol.

STERNBACH: Yes, it was made from biotin.

KOEPPEL: You got two patents. They were among your first patents, in 1949 (7).

STERNBACH: Yes. I got seven patents in the biotin field with Goldberg (8).

KOEPPEL: Were they issued to you or Hoffman-La Roche?

STERNBACH: To Dr. Goldberg and me. Here, patents are issued to people, and the people can sell it to the company.

KOEPPEL: I see.

STERNBACH: I think that was still the case lately. I can look it up there in the back.

KOEPPEL: Well, it says biotin and then it says Goldberg and Sternbach and then "to Hoffmann-La Roche." That's why I'm asking.

STERNBACH: Yes. It's shown in the title to whom the patent has been sold.

KOEPPEL: Now actually we should get into the big story which deals with the 1,4-benzodiazepines.

STERNBACH: Yes. Let's see how we make the transition.

KOEPPEL: Let me ask you about what I read. The company started to look for new compounds that would be useful as tranquilizers?

STERNBACH: Yes, that's correct.

KOEPPEL: And it says you had almost stumbled upon benzodiazepines.

STERNBACH: Not quite.

KOEPPEL: Oh. That's what I would like you to comment on.

STERNBACH: It was not immediately so. These were the times when the first tranquilizers appeared, Miltown first and then Chlorpromazine, Thorazine. Roche became very interested in these compounds because it was a new group of very useful drugs. In addition, it looked financially profitable. So at that time we became very interested in tranquilizers. We chemists were asked to submit proposals for the synthesis of tranquilizers which we then could follow up. So I submitted something and Dr.

Aeschlimann, who was our research director here at that time, let me work on these compounds. However, not much came out of that.

KOEPPEL: What was the nature of these compounds?

STERNBACH: These were phenothiazines with attached amino groups. But not much came out of that. Therefore I thought it might be worthwhile to start with a completely new group of compounds which would have no relationship to Miltown or to Thorazine or to anything that was known to have tranquilizing or sedative properties. In looking for such a group of compounds, I thought it would, for practical purposes, be very useful if this would not be a very well-known group of compounds but rather a group of compounds which were quite unexplored but readily accessible, and which could be readily converted into other compounds. In thinking about a practical approach, it occurred to me that I had worked with Professor Dziewonski on compounds which were at that time known as heptoxdiazines.

[END OF TAPE, SIDE 2]

STERNBACH: I came across these compounds during my work with Professor Dziewonski. That was in Cracow. We obtained these compounds in an attempt to transform amino ketones, like amino-benzophenones, by oxidation and a Beckmann rearrangement. I didn't expect that instead dehydration would occur, but a thorough literature search showed that it was known that these benzoheptoxdiazines can be formed under the reaction conditions we were using. These products crystallized very nicely and they seemed to be readily accessible because a multitude of benzophenones used as starting materials with various substituents in the aromatic nuclei could be easily prepared.

KOEPPEL: How did you get the idea that they could be tranquilizers?

STERNBACH: Oh, I didn't have an idea.

KOEPPEL: It was just a lucky guess?

STERNBACH: Yes. I just knew that they are new compounds. I looked through the literature about the known benzoheptoxdiazines and found that they were never tested for biological activity. So I resynthesized the compounds which I had made in Dziewonski's laboratory and submitted them for testing. It was found that they did not have any biological activity.

But since I liked this group of compounds, I planned to continue to work with these readily accessible benzoheptoxdiazines and prepare a few new ones. Since it's known that basic side chains very often impart biological activity, I thought it might be interesting to make benzoheptoxdiazines into which an amino group could be introduced. This means they would have to have a reactive halogen on a side chain. So I started to synthesize some of those compounds. They were quite readily accessible and crystallized well. This was very important because that made it possible to prepare within a relatively short time a large number of compounds.

So I synthesized some of these compounds with a chlorine in the side chain and reacted them with various secondary amines. You usually use secondary amines because it's known that cocaine, atropine, scopolamine, and other related compounds have a disubstituted amine in their basic moiety. Also the synthetic local anesthetics like novocain have basic side chains, as do the antihistamines. So I thought, well, we will try to introduce basic side chains into these benzoheptoxdiazines. I really synthesized quite a number of compounds which were submitted to Dr. Randall for pharmacological testing, but none of these were active.

Finally, Dr. Goldberg told me that I had worked enough with these compounds. "They don't lead you anywhere. Why don't you stop this and work on something more useful, like antibiotics?"

KOEPPEL: Was that in 1955?

STERNBACH: Yes, it was around 1955.

KOEPPEL: So you really gave up this work?

STERNBACH: Officially I gave up this work, but on the side we were still working on them a little bit. Mainly, however, we were working on antibiotics and on various other projects in which Goldberg was interested. It came to that point that the laboratory was completely filled up with various samples, crystalline and noncrystalline, mother liquors in Erlenmeyer flasks, in bottles and beakers. There was no working space available any more.

Then I told Earl Reeder, my co-worker, "Well, we will have to clean up. There is no other way out." So we had to clean up and we threw out what looked completely hopeless, but kept what looked half-hopeless. The compounds which crystallized we put into bottles and labeled them, according to our laboratory book numbers. While doing this, Earl came to me with two samples. One was a base and the other its hydrochloride. He said, "These compounds were still obtained from these benzoheptoxdiazines.

Should we throw them out or wouldn't it be worthwhile to submit them for testing?" So I said, "OK, let's submit the hydrochloride for testing."

I brought it to Goldberg. Goldberg had to sign all the data sheets. I signed my name and he as group chief had to sign. He signed the data sheet and said, "So, this is the last compound in the group of compounds which you really insisted on investigating." I said, "Yes." I also thought that this might be the last compound. I thought, it will be found inactive and then at least I can have a nice chemical publication. But, "siehe da" [Lo and behold!], it was completely different. That compound showed very interesting properties.

Dr. [Lowell O.] Randall tested it for anticonvulsant, sedative, and tranquilizing properties in various animal species, even in monkeys. Yes, it was even active in monkeys. He compared it with meprobamate (Miltown), which was at that time the tranquilizer. He also compared it with chlorpromazine and even with phenobarbital. It turned out that this compound had very interesting properties and in all the tests it was much more potent than Miltown. In some of the tests it was even as potent as phenobarbital. And compared with chlorpromazine, it was better in some of the tests and in others it wasn't as good. So it was worthwhile investigating. Randall asked for more of the compound and suggested, "Why don't you prepare a few analogs, or related compounds so we could establish which is the best product."

KOEPPEL: What was the laboratory book number of the compound? Was it RO 5-0690?

STERNBACH: Yes, that was it.

KOEPPEL: That was Librium?

STERNBACH: Yes, that was Librium.

KOEPPEL: Not only did you have a few good publications, you also had a good product.

STERNBACH: Yes.

KOEPPEL: You published about sixty papers on quinazolines and 1,4-benzodiazepines. Would you tell me that story where you identified a compound that was mislabeled?

STERNBACH: Yes, or misidentified.

KOEPPEL: Misidentified as a quinazoline or as a benzodiazepine?

STERNBACH: OK. I'll tell you and then we'll see whether there is something.

KOEPPEL: Am I jumping ahead here?

STERNBACH: Yes, you are.

KOEPPEL: All right. Then please go on.

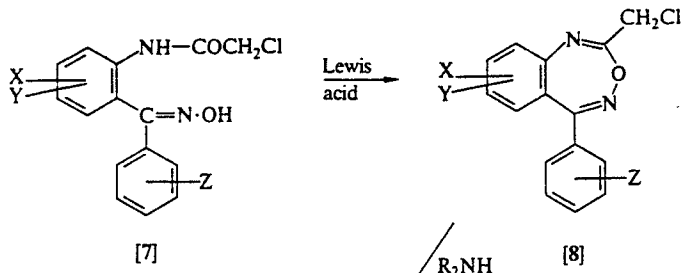
STERNBACH: We started to work with these compounds and submitted them for testing. We submitted the hydrochloride--that's when we had this cleaning up--and then we had these two compounds which Earl Reeder showed me and asked, "Shouldn't we test these compounds?"

KOEPPEL: And you had them tested?

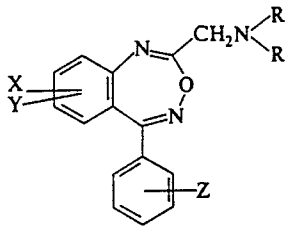
STERNBACH: Yes, then we had the hydrochloride tested and it was found it was active. But even then, we didn't know the structure of these compounds. The analysis checked out. We thought they were heptoxdiazines with a basic side chain. Later on we found out that our heptoxdiazines were not heptoxdiazines at all but were quinazoline N-oxides, which means they have a six-membered hetero-ring instead of the seven-membered ring present in heptoxdiazines.

KOEPPEL: I have it here in the booklet, "The Benzodiazepine Story" (9).

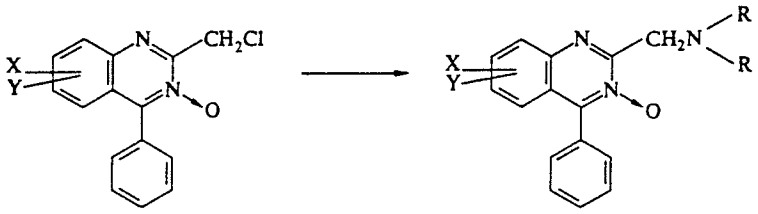
STERNBACH: Yes. It is on pages 10 through 14 [see following page]. You see, we originally thought the compound had structure [**8**]. It turned out it really didn't have this structure, but was a quinazoline-N-oxide of structure [**10**]. Then we reacted it with a secondary amine to obtain compounds of type [**11**]. That much we knew at the time when we reacted compound [**12**] with monomethylamine. And this reaction product showed these interesting biological properties. Then we established that it did not have the expected structure [**13**], but was the product of a rearrangement which yielded compound [**1**].



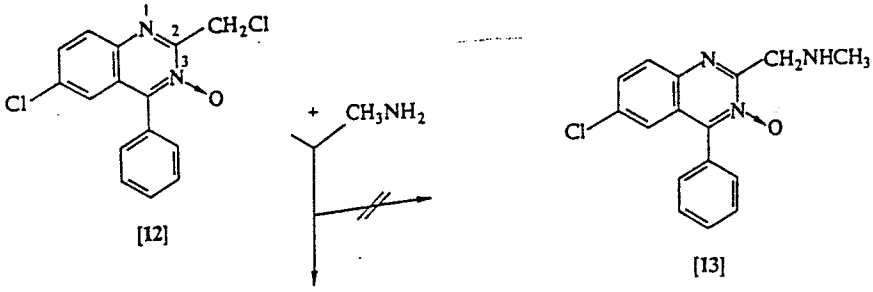
[7] [8]



[9]



[10] [11]



[12] [13] [1] [14] [15]

At that time it was rather difficult to establish the structure of this compound. We didn't have the physical-chemical possibilities which we have now. We had to do a total classical structure determination by degradation of the molecule and established beyond any doubt that this compound must have structure [**1**]. This was the compound which underwent very thorough pharmacological testing. It was particularly interesting because of its taming properties in monkeys. We found also that it had a very low toxicity. We prepared a number of analogs and decided to start clinical studies with one of these compounds. They had all approximately the same pharmacological properties, so we thought we might as well stick with compound [**1**] which was most readily accessible, its starting material being para-chloroaniline, which was a commercial product. We soon decided to study the chronic toxicity and prepare the product for clinical testing.

KOEPPEL: And you said, "Eureka, we found it."

STERNBACH: Yes. I have here a chronological list of the dates and events in the development of RO 5-0690 [see following page]. On May 7th, 1957 we submitted it for pharmacological testing. We had stopped our synthetic studies in 1955 and then in 1957 we submitted the product for testing.

KOEPPEL: You published over sixty papers in the series, "Quinazolines and 1,4-Benzodiazepines." Which one was the crucial paper on Librium?

STERNBACH: I think the crucial paper was number II (10) which describes the formation of Librium. (Paper I didn't have a number since we did not know then that there would be such a series.)

KOEPPEL: Paper IV describes Valium (11). You now began to study intensively.

STERNBACH: Yes. We found that Librium was quite unstable in aqueous solution. The solution soon became turbid. It decomposed slowly under the influence of acid. Now, this naturally interested us. We extracted the turbidity. We investigated it and found that this decomposition product had lost the methylamino group present in Librium. Instead of the methylamino group it had a carbonyl group in the 2- position, and it still had the N-oxide group. We removed the N-oxide group and found that this compound was still active.

A few important chronological data in the development of Ro 5-0690

May 7, 1957	Submitted for pharmcological testing. Data sheet.
July 26, 1957	Pharmacological activity reported by Dr. Randall and Mrs. Kappell, RCR #11788.
Sept. 24, 1957	Discussed at Advisory Group to Research Steering Committee. Shift planned from hydrochloride to more stable base for toxicity and ultimately clinical testing.
March 19, 1958	I.O. Dr. Bagdon to Dr. Randall. Comparison of toxicity to RO 5-0690 with Ro 5-0690/1 (free base). Hydrochloride RO 5-0690 less toxic. Base caused local intestinal irritation.
April 15, 1958	Structural proof reported by Sternbach in RCR #4328.
April 25, 1958	Analytical Data Sheet Dr. Wollish RCR #12308.
April 30, 1948	Preliminary Pharmacology Data Sheet Dr. Randall RCR #12189.
May 15, 1958	Patent application filed for 1,4-Benzodizepine 4-Oxides.
June 5, 1958	Clinical Data Sheet, S. R. Gustafson RCR # 12677.
June 18, 1958	Preliminary clinical studies started under Dr. Chapman.
Dec. 22, 1958	1-year chronic toxicity studies started by Dr. Bagdon.
July 7, 1959	Intensive clinical studies started by Dr. Hines near end of 1958. Patent issued.
September 1959	Princeton meeting.
November 1959	Galveston meeting.
February 1960	Introduced.
April 8, 1960	Luncheon.
April 1961	Chemical paper. Submitted April 1960.
July 7, 1976	Patent expires.

First pharmacology activity 1957, introduced February 1960 - 2 1/2 years.

KOEPPEL: Was there turbidity without the oxide group?

STERNBACH: The solution became turbid because the product decomposed to give a water-insoluble compound, benzodiazepine-4-oxide, which however still had the same activity. Now we went on and modified it even more. We removed the oxygen attached to the nitrogen and this compound was still active. Then we tried to vary the groups on the nitrogen. We made a number of such compounds and also varied the substituents in the aromatic ring until we had about twenty compounds on hand. That was in December 1959.

KOEPPEL: They are all shown in table 6 [see following page].

STERNBACH: Most of them, but the table shows all the compounds which were on the market in the United States at the time I wrote this monograph (9).

KOEPPEL: But you tested many, many more.

STERNBACH: Oh, many, many more compounds. In December of 1959 we had a number of compounds on hand. Dr. Randall and I decided that we would have to propose another compound to be prepared for clinical testing. This involved more intensive toxicity studies and a study of its properties in various animal species. So we looked at all our data but no compound was significantly different from the other. Only the potency varied and only minor differences in the spectrum of activity were noticeable. The most potent compound was the one which had a methyl group in the 1- position. So we proposed this for further clinical testing. This compound then became Valium and diazepam is the generic name.

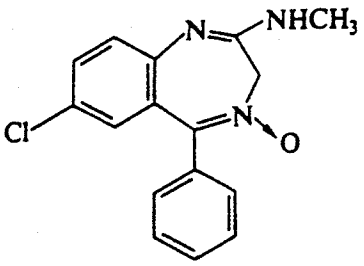
KOEPPEL: It was officially announced in 1963?

STERNBACH: It was introduced in 1963. We had it in 1959, and the whole thing started then to move very rapidly [see the second following page for important dates].

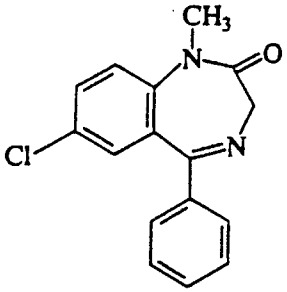
KOEPPEL: I see.

STERNBACH: We were very careful with our publications. We did not publish anything before the patent appeared. Usually you can publish as soon as you have applied for the patent, because you are protected from that moment on. But in order not to divulge

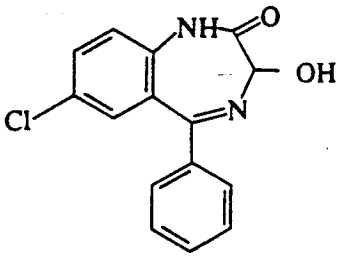
Table 6
Benzodiazepines marketed in the United States



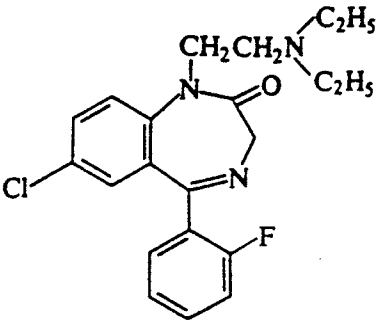
[1] Chlordiazepoxide
(‹Librium›, 1960)



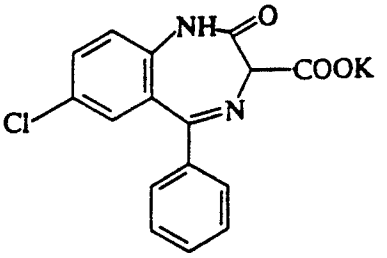
[2] Diazepam*
(‹Valium› Roche, 1963)



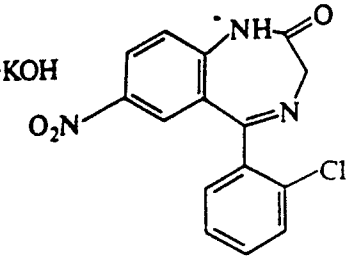
[29] Oxazepam
(‹Serax›, 1965)



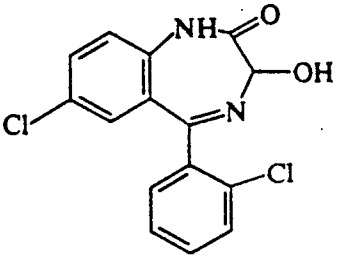
[105] Flurazepam
(‹Dalmane›, 1970)



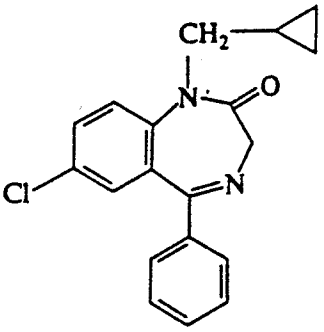
[40] Clorazepate
(‹Tranxene›, 1972)



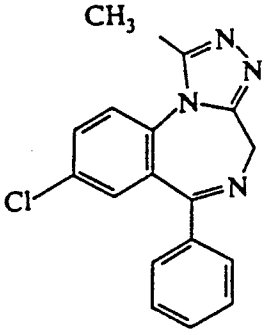
[106] Clonazepam
(‹Clonopin›, 1975)



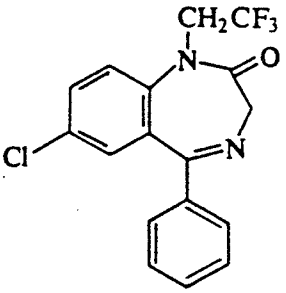
[107] Lorazepam
(‹Ativan›, 1977)



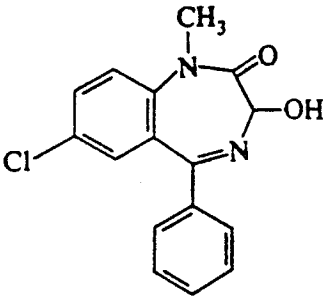
[108] Prazepam
(‹Centrax›, 1977)



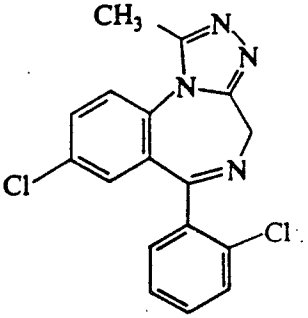
[66a] Alprazolam**
(‹Xanax›, 1981)



[109] Halazepam
(‹Paxipam›, 1981)



[110] Temazepam
(‹Restoril›, 1981)



[66b] Triazolam**
(‹Halcion›, 1982)

Valium

Oct. 26, 1959 First made with diazomethane. RN 161.

Nov. 27, 1959 Chemical Data sheet. Analysis Nov. 16. 2046.

Dec. 10, 1959 Patent application.

1. Animal tolerance studies authorized - see RSC No. 1/60 Dated January 7, 1960. started Feb. 10, 1960.

2. Long Term Chronic Toxicity Trials authorized February 11, 1960 - see RSC No. 5/60.

3. Pharmacological data sheet May 3, 1960 - see Randall RCR 14,308.

4. Given to Dr. Abrams May 10, 1960.

5. Preliminary clinical trials authorized May 12, 1960 - see RSC 15/60.

6. Chronic toxicity in dogs authorized September September 29, 1960 - see RSC 33/60.

7. Clinical data sheet March 27, 1961 - Gustafson, Gordon - see RCR 11,245.

8. Dr. Bagdon RCR 14952, October 25, 1961.

9. NDA December 15, 1961.

10. Introduced December 1963.

11. Patent issued February 27, 1968, U.S. 3,371,085.

First tested November 1959, introduced December 1963 - over 4 years.

important information prematurely, we waited always until something in print had appeared.

KOEPPEL: You had a great number of patents on these benzodiazepines.

STERNBACH: Yes, also on related compounds and on various transformations of benzodiazepines.

KOEPPEL: You also discovered Mogadon in 1965 [see Table 7, following page]. It's not marketed in the United States. Do you know why?

STERNBACH: They had difficulties in the beginning and then they decided they would introduce Dalmane instead, which is a different compound.

KOEPPEL: Are they hypnotics instead of tranquilizers?

STERNBACH: Yes.

KOEPPEL: From what I see, the difference is mainly the nitro group in the 7- position of the first ring?

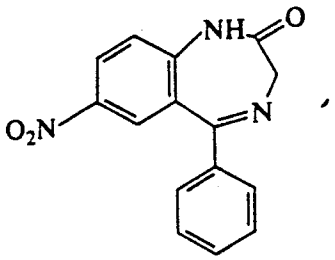
STERNBACH: Yes. The difference is in the nitro group.

KOEPPEL: And that makes so much difference?

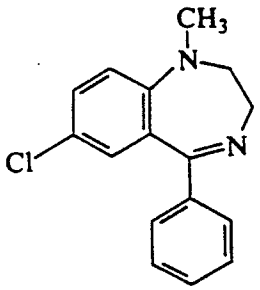
STERNBACH: I wouldn't say that it's so much. You see, it's a curve. On the lower point of the curve you would put the sedatives. If the sedative properties increase significantly, then the products become hypnotics. The substituent in the lower ring has also a very significant effect as you can see in compound [**112**], Rohypnol, which is on the market in Switzerland and is a very potent hypnotic. It has a fluorine in the phenyl ring. We see this substituent also in Dalmane, compound [**105**]. The generic name is flurazepam. We have a chlorine in the phenyl ring in clonazepam, compound [**106**]. Clonazepam (Clonopin) is called Rivotril in Switzerland and is marketed as an anticonvulsant.

KOEPPEL: Which ones are especially attributed to you?

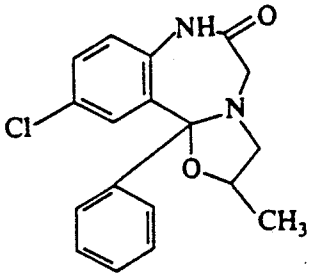
Table 7
Benzodiazepines marketed in countries other than the United States



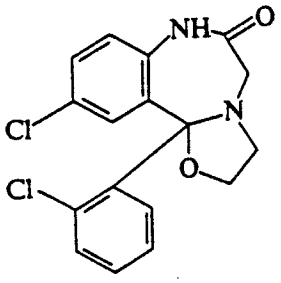
[111] Nitrazepam*
(‹Mogadon›, 1965)



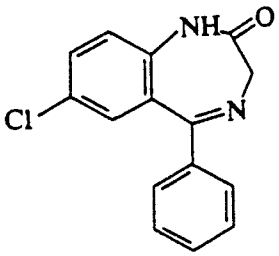
[42] Medazepam
(‹Nobrium›, 1968)



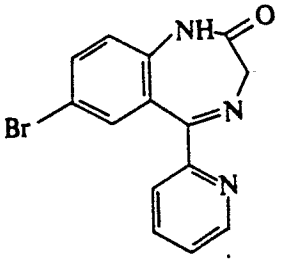
[59a] Oxazolam
(‹Serenal›, 1971)



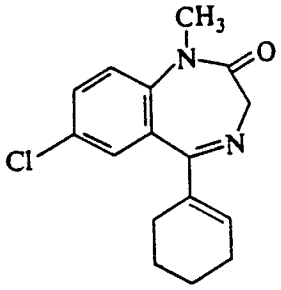
[59b] Cloxazolam
(‹Sepazon›, 1974)



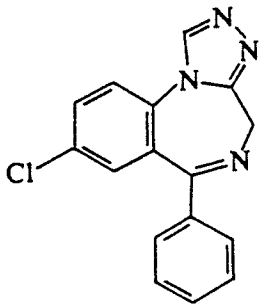
[23] Desmethyldiazepam*
(‹Madar›, 1973)



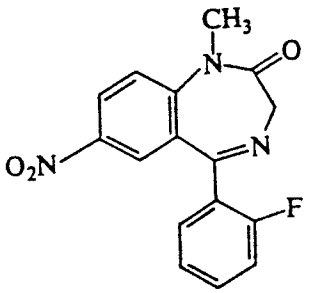
[50] Bromazepam
(‹Lexotanil›, 1974)



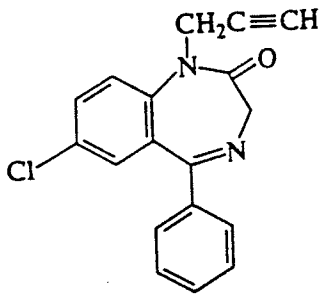
[54] Tetrazepam
(‹Myolastan›, 1974)



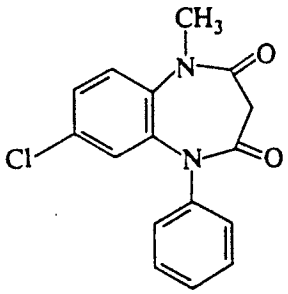
[65] Estazolam
(‹Eurodin›, 1975)



[112] Flunitrazepam
(‹Rohypnol›, 1975)



[113] Pinazepam
(‹Domar›, 1975)



[86a] Clobazam
(‹Urbanyl›, 1975)

STERNBACH: Only compounds [**1**], [**2**], [**23**], [**42**], [**50**], [**105**], [**106**], [**111**], and [**112**] are ours.

KOEPPEL: But they have mainly been developed by you.

STERNBACH: The ones I just mentioned, yes. You see, of all the substitutions in position three were done by other companies in order to obtain products which were not protected by our patents.

KOEPPEL: I see.

STERNBACH: We never worked on them because we didn't find them too interesting.

KOEPPEL: So there was actually a big race between the pharmaceutical companies.

STERNBACH: Yes. You see, Librium came out in 1960 and Valium in 1963. Serax, the first competition by Wyeth, came out in 1965. Then we brought Dalmane out. Next was Tranxene, which is not ours. I forget the company which has Tranxene. And then Clonopin is ours. But Lorazepam and all the compounds with an OH group are Wyeth's. Then we made a compound which is sold very much in Switzerland. That is Lexotanil or Lexotan, compound [**50**]. It's on the market in Switzerland and in other countries too. Here it's still in the hands of the FDA. I don't know whether we'll ever get it.

KOEPPEL: Do we know the effect of Valium on the central nervous system?

STERNBACH: They think it acts on the lymphatic system. They are now studying receptor sites and points of attachment and also compounds which displace each other in the brain. Basel has an interesting compound which displaces Valium from the attachment point and so reverses the effect of Valium. For instance, if you put somebody to sleep with Valium, and you want to stop its effect, then you inject the other compound that is inactive and replaces Valium. It is an "anti-Valium" so to say, an "anti-benzodiazepine."

KOEPPEL: On the methodology and rationale behind molecular modification, would one consider it a rather haphazard approach today, or is it still used in the same way?

STERNBACH: I think it's still used in the same way. If you make compounds which have biological activity, then you first study what changes in the molecular structure affect this activity.

KOEPPEL: I see.

STERNBACH: Let's say you study the relationship between changes and biological effect. That's what we did. Then we came up with certain regularities which are shown in this table [see following page].

KOEPPEL: I found that ring A, when substituted in the 7-position...

STERNBACH: Yes, the substituent in position seven was crucial. An electron-withdrawing substituent like chlorine or the nitro group increased the activity whereas electron-releasing substituents like the CH_3 group or the CH_3O group decreased the activity very significantly.

KOEPPEL: I see. So one knows pretty much how to design it.

STERNBACH: We now know how to design it.

KOEPPEL: But in those days...

STERNBACH: In those days it was all based on the testing results.

KOEPPEL: It was all trial and error?

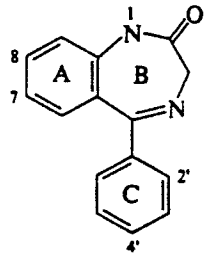
STERNBACH: Oh, yes. Completely. In the lower phenyl ring, we knew very soon that the substituent in the para position almost abolished activity. Almost. Whereas a halogen in the ortho position increased activity significantly. You would think ortho and para are very similar, but they are not. They are completely different.

KOEPPEL: You had to sacrifice a great number of animals in the laboratory to do the testing.

STERNBACH: I guess so.

Table 4*

Pharmacological properties of some representative 5-phenyl-1,4-benzodiazepinones



Substituent in position						Pharmacological activity					
Compound	1	7	8	2′	4′	Inclined screen	Foot shock	Cat	Metrazol	Maximum	Minimum
a						150	100	30	800	30	75
[23]		Cl				75	20	1	6	25	61
b			Cl			>500	>100		334	150	800
c		CH_3				>500	>100		175	167	>800
[2]	CH_3	Cl				30	10	0.2	1.4	6.4	64
d	$CH_2CH(CH_3)_2$	Cl				200	50	20	8.5	50	>800
e	$C(CH_3)_2$	Cl				>500	>100		>800	600	>800
f	$CH_2CONHCH_3$	Cl				450	80	20	0.5	15	85
g		Cl			Cl	>500	>100		>800	300	>800
h=[116]		Cl		Cl		100	40	0.1	0.4	13	115
i		Cl		F		40	5	0.05	0.08	1.5	50
j		CF_3				10	10	0.1	1	5	21
k		N_3				15	15	1.2	4.6	8	40
[111]		NO_2				15	5	0.1	0.5	8.4	132
[112]	CH_3	NO_2		F		1	0.8	0.02	0.12	12	345

* All the data shown in this table except those for compounds e, g and i are reported in STERNBACH et al.[117,118], some also in CHILDRESS et al.[20]. References to the preparation of the compounds are quoted in STERNBACH et al.[118,119].

KOEPPEL: This is not done so much today.

STERNBACH: Not so much and it is wrong, because you see best in the animal what the compound does. You can't do that mathematically.

KOEPPEL: You think that animal testing is absolutely necessary?

STERNBACH: Yes, it is very important. I think it's very much neglected now in favor of biological testing which never gives you all the information you want.

KOEPPEL: They have started some in vitro testing, like at Johns Hopkins Medical School. Do you think that's going to be successful?

STERNBACH: They do it in vitro. I'm not a great believer in in vitro testing. Yes, they have the receptor sites now. You know they can isolate receptor sites and see whether there is a binding between the active drug and the receptor site by some turbidity in the solution. But I'm a great believer in testing in animals and for these testings you have to find first a compound or a group of compounds which would show activity in animals. This you can only achieve by testing in animals. Then you can continue your studies.

KOEPPEL: Otherwise you have no knowledge about structure-activity relationships.

STERNBACH: Yes. We found this by testing in animals.

KOEPPEL: Yes, of course. You must have had a good team to work with you on this.

STERNBACH: Well, I had a good group of chemists working with me.

KOEPPEL: Are there some people that should be especially mentioned?

STERNBACH: Well, at that time Dr. [Ian] Fryer and Dr. [Werner] Metlesics worked closely with me. Earl Reeder was with me even before the benzodiazepine era, from the very beginning on when I had only my own laboratory to work with.

KOEPPEL: By that time you were the group leader.

STERNBACH: First I had my own laboratory. Then I became a group chief.

KOEPPEL: And then you became director of medicinal chemistry in 1966. So then you were really in charge of the whole research program in medicinal chemistry.

STERNBACH: Yes, but I really limited myself to the benzodiazepines. I left other areas to the chemists who did the work.

KOEPPEL: Well, I think we have a pretty good idea now about your work on Valium and Librium and related compounds. I would like to ask a few questions of a more philosophical and perhaps clinical nature. I read in an interview that you gave ten years ago in Parade that you considered Valium to be fairly non-addictive (12). Would you like to comment on this?

[END OF TAPE, SIDE 3]

KOEPPEL: Do you think it's being abused, or not always used for what it was designed?

STERNBACH: It might be possible that for a while it was a street drug. I don't know whether it still is or not.

KOEPPEL: It was a housewife's street drug.

STERNBACH: They might have used more than was really necessary.

KOEPPEL: Doctors also prescribed it liberally.

STERNBACH: Yes, very often. It saved them a lot of time. They didn't have to spend so much time with the patient and they gave a prescription and the prescription did what was really needed. But I don't think it's overdone now. The doctors are now well aware of the situation.

KOEPPEL: Yes. They're very careful now. They're very cautious. It's also very much restricted. You can't refill it.

STERNBACH: No, you can't refill. I think the doctor has to write a new prescription in order to have it refilled.

KOEPPEL: Well, it certainly is a wonder drug and I am sure that the financial rewards for Hoffmann-La Roche were tremendous for these products.

STERNBACH: Yes, they were.

KOEPPEL: What about you? I understand you sold the patent for one dollar (13).

STERNBACH: Yes. That's what it was. I got very nice salary increases and extra benefits and now whenever I want to go to a congress I just have to tell our research director, and he says, "Oh, yes. La Roche will pick up the tab." I'm getting an honorary doctorate in Frankfurt this June.

KOEPPEL: Yes. That's wonderful.

STERNBACH: I asked Dr. [Ronald] Kuntzman, our research director, "Can my wife and I go and can we go business class?" He said, "Oh yes, sure. Roche will cover the expenses." This even came from Basel. It came via Grenzach, Germany which was contacted by Frankfurt that I'm getting the honorary doctorate. Professor [Ernst] Mutschler or Professor [Herbert] Oelschläger, one of the professors there, asked Roche if they would pick up the trip expenses for the Sternbachs to come to Frankfurt. Our expenses in Germany will be covered also.

KOEPPEL: So you have no regrets that you didn't own the patent?

STERNBACH: No. Well, I could have gotten much more, but on the other hand I don't need more. I do not have very expensive hobbies. I can afford whatever I want to do.

KOEPPEL: What are your hobbies?

STERNBACH: Well, it used to be skiing. I don't do much skiing any more. I do only cross country skiing and I like to spend my vacations with my family. I invited both my sons with their

families to St. Croix for a week. So, I can afford that. This summer I will go to Switzerland in connection with my trip to Frankfurt.

KOEPPEL: You go to Switzerland often, don't you?

STERNBACH: Yes, we go almost every year.

KOEPPEL: But you don't have a place to live there.

STERNBACH: We have a small rented one-room apartment in Zürich. It's very cheap. It's something around five hundred francs a month. My wife said she wouldn't go to Europe if she didn't have a place where she can go to directly and stay. That's what we are using now. We will go there first and then we will go by train to Frankfurt. After that we will go to Pontresina for a week. I also invited one of my sons and his family.

KOEPPEL: Is one of your sons in Zürich now?

STERNBACH: No, they are both here.

KOEPPEL: He's not at the ETH?

STERNBACH: No. He was there for a while with Professor [Albert] Eschenmoser.

KOEPPEL: I saw some of his publications with Eschenmoser.

STERNBACH: Yes. He's now an Assistant Professor at Duke University and he is presently looking for an industrial job and he might join Merck. It's just in the air. [He joined Glaxo in 1987.]

KOEPPEL: Now the patent for Valium has expired.

STERNBACH: Yes, this patent expired.

KOEPPEL: That patent was for twenty years?

STERNBACH: No, it's for seventeen years. We were very lucky with Valium because Wyeth was fighting us and we got the patent six years later than we should have gotten it.

KOEPPEL: I see. So you had it for a longer time.

STERNBACH: Yes, we got it for a much longer time. It expired in February of last year.

KOEPPEL: Do you think there will be a lot of sales under the generic name?

STERNBACH: Yes, there are generic Valiums--diazepams--on the market. The name is naturally protected for us. It has to be called something else.

KOEPPEL: Is it much cheaper?

STERNBACH: It's much cheaper. For some of the insurance programs you have to prescribe the cheapest drug or the pharmacy has to give you the cheapest equivalent.

KOEPPEL: It seems to be cheaper in Switzerland than in the United States.

STERNBACH: Yes. It probably is. Do you mean Valium itself?

KOEPPEL: Yes. Is Hoffmann-La Roche trying to design new drugs to get new patents along the same line?

STERNBACH: With the benzodiazepines I think that we are fairly finished.

KOEPPEL: Are you doing something else that's interesting and important?

STERNBACH: No, not really. My research consisted in working at the bench in the laboratory and discovering some things that way, but not on paper. I think on paper you don't invent that much. At least, I am not very good at it.

KOEPPEL: Well, what do you think is the future of drug research? We hear so much about immunology and genetic

engineering. Do you think that the old molecular modification drug, or should I say, design drug, is a thing of the past?

STERNBACH: No. This is a very good question, because people act as if only molecular biology or genetics could lead to new drugs. I think there is still the possibility of inventing drugs as we invented the benzodiazepines, or as the sulfa drugs were invented. Of course, people say the chances are very small. But then, if you find something, it will be something completely new. If you work with modifications of old drugs, then you can only find drugs which are similar to those. You have to look into new classes of chemical compounds in order to find something new. There is no reason why compounds which are completely different from the ones which are now being investigated, could not have some important biological activity.

KOEPPEL: Yes, and since we know much more about the effect of substituent groups we...

STERNBACH: Well, you cannot extrapolate this. If you know the effect in the benzodiazepine series, that's one thing. That is valid for the benzodiazepine series only. In antihistaminics or anticholinergics the substitution rules are different. The effect of the substituent on the activity is different, in every class of compounds it's different.

KOEPPEL: Are computers used to design drugs?

STERNBACH: Well, possibly they are, but I don't think they will lead to very much. You can't feed into it what you do not know. You get "garbage in, garbage out"--nothing in, nothing out.

KOEPPEL: I would like to talk a little bit about your many awards and honors. Your curriculum vitae lists a number of awards. Among them are the American Chemical Society Award in Medicinal Chemistry in 1978, the ACS Award for Creative Invention in 1979, and the Carl-Mannich-Medal from the German Chemical Society in 1984. You have an honorary Doctor of Technical Sciences from the Technical University in Vienna and an honorary Doctor of Science degree from Centenary College in Hackettstown, New Jersey. Now you're going to get the doctor phil. nat. honoris causae from the Johann Wolfgang Goethe-University in Frankfurt. And this is just from a long list of honors.

STERNBACH: I think the John Scott Medal Award from Philadelphia in 1982 was also a nice thing.

KOEPPEL: Is there anything else you would like to add from this list?

STERNBACH: Well, the honorary doctorates, like the one from Vienna in 1971, and the one I'm getting now in Frankfurt, are especially important.

KOEPPEL: You have over a hundred and twenty publications and five monographs. You also have over two hundred and thirty U.S. patents.

STERNBACH: Yes. I emphasize this as U.S. patents, because all these patents then appeared in maybe twenty or thirty, in some cases, fifty different countries. So I have that many patents in various countries. The original ones are all U.S. patents.

KOEPPEL: And I'm also looking at your practical contributions as listed in your curriculum vitae. We have already discussed the technical synthesis of biotin. You also made Arfonad.

STERNBACH: Yes, it's an intermediate in the biotin synthesis. It's a ganglionic blocker and it's still being used. Well, what does it do really? It lowers the blood pressure and is a very short-acting agent used in "bloodless surgery." Another product is an anticholinergic agent used against ulcers. Quarzan is this compound which is contained in Librax. Librax is a mixture of Quarzan and Librium.

KOEPPEL: You also have Librium, Valium, Nobrium, Lexotanil, Mogadon, Dalmane, Rohypnol, and the anticonvulsant, Clonopin.

STERNBACH: Which is marketed in Switzerland as Rivotril.

KOEPPEL: Would you like to add anything else to this interview?

STERNBACH: No. We have everything from the monograph and we discussed my youth and my growing up.

KOEPPEL: What are you going to do now? You're still a consultant for Hoffmann-La Roche. Do you plan to go on with that?

STERNBACH: Yes. They don't consult me very much but at least I have a space where I can keep my books, write, and use the library.

KOEPPEL: You have an office. Do you have your own secretary?

STERNBACH: No. That I have to share. Somehow I usually get somebody who does things for me.

KOEPPEL: But you still come in early in the morning.

STERNBACH: Yes.

KOEPPEL: You are amazingly energetic.

STERNBACH: Well, my best working hours are the morning hours. Later on my brain power goes down!

KOEPPEL: Well, Dr. Sternbach, this concludes our interview. I would like to thank you so much for your cooperation and the fascinating account of your interesting life.

STERNBACH: Thank you for your thanks. It was really a pleasure to talk with you and to tell you all about myself.

[END OF TAPE, SIDE 4]

NOTES

A complete list of the publications and patents of Leo Sternbach may be found in the Beckman Center Oral History File #0043.

1. K. Dziewonski, C. Baraniecki, and L. H. Sternbach, "A New Method for the Preparation of Thioindigo Dyes. I. Syntheses in the Naphthalene Group," Bulletin International de l'Academie Polonaise des Sciences et des Lettres, Classe des Mathematiques et Naturelles, Series A: SciencesMathematiques, (1930A): 198-202.

2. K. Dziewonski and L. H. Sternbach, "The Reaction Between Benzoyl Chloride and alpha-Naphthylamine," Bulletin International de l'Academie Polonaise des Sciences et des Lettres, Classes des Mathematiques et Naturelles, Series A: Sciences Mathematiques, (1935A): 327-332; K. Dziewonski and L. H. Sternbach, "Pyrene," Roczniki Chemii, 17 (1937): 101-104.

3. Wo. Pauli and L. H. Sternbach, "Comparative Electrochemical Studies of Highly Purified Lyophilic Sols. VI. Electrochemistry of Sols of Alginic Acid," Kolloid-Zeitschrift, 84 (1938): 291-303.

4. Sigmund Frankel, Die Arzneimittel Synthese (Berlin: Julius Springer Verlag, 1927).

5. Wo. Pauli and L. H. Sternbach, "Electrochemistry of the Agar Sol," Helvetica Chimica Acta, 24 (1941): 317-339.

6. L. Ruzicka and L. H. Sternbach, "Diterpenes. XXXIV. Origin and Degradation of Tetrahydroxyabietic Acid," Helvetica Chimica Acta, 21 (1938): 565-583.

7. M. W. Goldberg and L. H. Sternbach, "Synthesis of Biotin," U.S. Patent 2,489,232, issued 22 November 1949 (application filed 31 May 1946); Goldberg and Sternbach, "Synthesis of Biotin," U.S. Patent 2,489,235, issued 22 November 1949 (application filed 24 July 1947).

8. M. W. Goldberg and L. H. Sternbach, "Imidazolido-tetrahydrofurans," U.S. Patent 2,489,233 issued 22 November 1949 (application filed 26 April 1947); Goldberg and Sternbach, "Thiophanes and the Method for Their Production," U.S. Patent 2,489,234 issued 22 November 1949 (application filed 16 July 1947);Goldberg and Sternbach, "Synthesis of Biotin and Related Compounds," U.S. Patent 2,489,236 issued 22 November 1949 (application filed 24 July 1947);Goldberg and Sternbach, "3,4-(2'-Keto-Imidazolido)-2- -hydroxy-pentyl-thiophanes," U.S. Patent 2,489,237 issued 22 November 1949 (application filed 8 June 1948); Goldberg and Sternbach, "Debenzylation of Benzylated

Imidazolido-thiophane Compounds," U.S. Patent 2,489,238 issued 22 November 1949 (application filed 8 June 1948); see also note 7.

9. L. H. Sternbach, The Benzodiazepine Story (Basle, Switzerland: F. Hoffman-La Roche & Co., 1980; second edition 1983).

10. L. H. Sternbach and E. Reeder, "Quinazolines and 1,4-Benzodiazepines. II. The Rearrangement of 6-Chloro-2-chloromethyl-4-phenylquinazoline 3-Oxide into 2-Amino Derivatives of 7-Chloro-5-phenyl-3H-1,4-benzodiazepine 4-Oxide," Journal of Organic Chemistry, 26 (1961): 1111-1118.

11. E. Reeder and L. H. Sternbach, "Quinazolines and 1,4-Benzodiazepines. IV. Transformations of 7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-Oxide," Journal of Organic Chemistry, 26 (1961): 4936-4941.

12. L. Shearer, "The Man Who Invented Valium," Parade, (27 June 1976): 8-10.

13. E. Reeder and L. H. Sternbach, "5-Aryl-3H-1,4-Benzodiazepin-2(1H)-Ones," U.S. Patent 3,371,085, issued 27 February 1968 (application filed 10 December 1959).

INDEX

A few important chronological data in the development of Ro 5-0690

May 7, 1957	Submitted for pharmcological testing. Data sheet.
July 26, 1957	Pharmacological activity reported by Dr. Randall and Mrs. Kappell, RCR #11788.
Sept. 24, 1957	Discussed at Advisory Group to Research Steering Committee. Shift planned from hydrochloride to more stable base for toxicity and ultimately clinical testing.

March 19, 1958	I.O. Dr. Bagdon to Dr. Randall. Comparison of toxicity to R0 5-0690 with Ro 5-0690/1 (free base). Hydrochloride R0 5-0690 less toxic. Base caused local intestinal irritation.
April 15, 1958	Structural proof reported by Sternbach in RCR #4328.
April 25, 1958	Analytical Data Sheet Dr. Wollish RCR #12308.
April 30, 1948	Preliminary Pharmacology Data Sheet Dr. Randall RCR #12189.
May 15, 1958	Patent application filed for 1,4-Benzodizepine 4-Oxides.
June 5, 1958	Clinical Data Sheet, S. R. Gustafson RCR # 12677.
June 18, 1958	Preliminary clinical studies started under Dr. Chapman.
Dec. 22, 1958	1-year chronic toxicity studies started by Dr. Bagdon.
July 7, 1959	Intensive clinical studies started by Dr. Hines near end of 1958. Patent issued.
September 1959	Princeton meeting.
November 1959	Galveston meeting.
February 1960	Introduced.
April 8, 1960	Luncheon.
April 1961	Chemical paper. Submitted April 1960.
July 7, 1976	Patent expires.

First pharmacology activity 1957, introduced February 1960 - 2 1/2 years.

Valium

Oct. 26, 1959 First made with diazomethane. RN 161.

Nov. 27, 1959 Chemical Data sheet. Analysis Nov. 16. 2046.

Dec. 10, 1959 Patent application.

1. Animal tolerance studies authorized - see RSC No. 1/60 Dated January 7, 1960. started Feb. 10, 1960.
2. Long Term Chronic Toxicity Trials authorized February 11, 1960 - see RSC No. 5/60.
3. Pharmacological data sheet May 3, 1960 - see Randall RCR 14,308.
4. Given to Dr. Abrams May 10, 1960.
5. Preliminary clinical trials authorized May 12, 1960 - see RSC 15/60.
6. Chronic toxicity in dogs authorized September September 29, 1960 - see RSC 33/60.
7. Clinical data sheet March 27, 1961 - Gustafson, Gordon - see RCR 11,245.
8. Dr. Bagdon RCR 14952, October 25, 1961.
9. NDA December 15, 1961.
10. Introduced December 1963.
11. Patent issued February 27, 1968, U.S. 3,371,085.

First tested November 1959, introduced December 1963 - over 4 years.