Obituary

In memorium Igor Torgov: Torgov’s way to total steroid synthesis

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ABSTRACT

The “Torgov reaction” opened an original pathway for the total chemical synthesis of steroid hormones, which is still used for the large-scale industrial production of steroid hormones at factories of Schering AG in Berlin, Germany.

Professor Dr. Igor Vladimirovich Torgov (1912–2007) was a well-known and brilliant bioorganic chemist of the 20th century [1]. He was especially acclaimed for his development of the novel reaction sequence for total synthesis of steroid hormones [2], which appears in the chemical literature with his name [3] as the “Torgov reaction sequence”, “Torgov cyclization”, “Torgov chemistry”, “standard Torgov procedure”, “Torgov-type intermediate, and carbocation”, “Torgov reagent and (+)-Torgov diene”, and “Torgov’s synthesis of estrone” [3]. The “Torgov reaction” opened an original pathway for the total chemical synthesis of steroid hormones, which is still used for the large-scale industrial production of steroid hormones at factories of Schering AG in Berlin, Germany. His scientific career of 67 years was interrupted twice. The first was during Stalin’s Great Purges in 1937–1938, when he was imprisoned for 1.5 years in the Black Lake Gulag in Kazan (Tatarstan, Russian Federation), the place of his birth in 1912. He was jailed as a result of an anecdote he told to students. The second interruption came during the Second World War in 1941–1945, when he served in the Red Army resisting the German invasion. His father was born in a family of Polish noblemen, banished to Kazan after the Polish revolt of 1863. Torgov’s father served as a General in the White (anti-Bolshevist) Army which was defeated in the Russian Civil War (1918–1921). His mother came from a family of Ryazan Tatars. Despite the bitter prison experience of the gulags, his will and motivation in science remained strong. He had studied chemistry in the Chemical School of Kazan State University which produced a number of great chemists. Possessing a brilliant memory and a powerful mind, Torgov received extensive training in various fields of organic chemistry while in Kazan. Academician Boris Arbuzov later noted that Igor Torgov passed the Kazan Chemical School examinations on organic chemistry more impressively than anyone else in the 20th century. In Kazan, Igor Torgov developed a strong ambition for work in fine organic synthesis.

He resumed advanced studies in Moscow at the Institute of Organic Chemistry of U.S.S.R. Academy of Sciences. In Moscow, he brilliantly passed the entrance examination on organic chemistry before a committee led by academician Alexander Nesmeyanov – a future President of U.S.S.R. Academy of Sciences. Torgov’s work at the Moscow Institute of Organic Chemistry was interrupted for 3 years during World War II. After demobilization from the Red Army in 1944, Torgov returned to Nazarov’s laboratory at the Institute to continue work on his thesis. Professor Ivan Nazarov was working in the acetylene chemistry at that time. In Nazarov’s lab, Igor Torgov completed the first synthesis of important chemical compounds such as vinylylcarbinol and divinylketone. In 1947, he completed and defended his PhD Thesis. The rich synthetic possibilities of acetylene chemistry allowed Torgov to study syntheses of complex polycyclic ketones related to natural compounds, in particular steroids. Torgov’s D.Sc. dissertation (1953) resulted from this 6-year research project. In 1958, academician M.M. Shemyakin invited Igor Torgov to lead the laboratory of steroid chemistry at his Institute of Chemistry of Natural Products of the U.S.S.R.’s Academy of Sciences, newly organized in Moscow. Working there, I.V. Torgov pioneered a reaction sequence for total synthesis of steroids after discovering a reaction that allowed creation of the steroid nucleus, the now famous Torgov reaction.

The Torgov reaction sequence used in total steroid synthesis is remarkably short [2] (Fig. 1). First, vinylcyclohexenols (I) react with cyclic diketones (II) resulting in polycyclic dienic diketones (III). Reaction between compounds (I) and (II) yielding diketones (III) was carried out in methanol under neutral or basic conditions depending on structure, the highest yield being with aromatic carbinals and cyclopentanone diketones (n = 1, 2; and R = substituent). This reaction was followed by an acid-catalyzed cyclization of intermediates (III) which resulted in the 14-hydroxy compounds (IV) which were then transformed into steroids (V).
cyclization is rapid due to facile conversion of III to the \( \Delta^{8,9} \) isomer and cation-olefin addition. \( \Delta^{8,14} \) diene V serves as starting points for the synthesis of a number of steroid hormones including estrol and estradiol derivatives. At the final stages of complete steroid synthesis, Torgov and co-workers had solved the problem of stereoselective reduction of double bonds of C and D cycles of substance like III by catalytic hydrogenation and reduction by alkaline metal in ammonia to compounds type IV and V. Further, to avoid a formation of racemic mixture of \(-d\) and \(-l\)-isomers as compounds I–V (biologically active are only \(-d\)-isomers) Professor Torgov developed an enantioselective reduction of intermediate ketone IIIa by \textit{S. cerevisiae} yeast culture resulting in compound VI. Thus, Igor Torgov was able to proceed with chiral intermediates such as compounds VII and VIII, to obtain, for example, d-estradiol in up to 90% yield.

After papers on total steroid synthesis and related topics published by Igor Torgov and co-workers [2], it became possible to synthesize steroid hormones possessing a wide spectrum of biological activity, in particular d-estradiol, 19-nortestosterone, 14-hydroxysteroids, and even 18-substituted examples. German scientists and technologists have also modified the Torgov reaction sequence to produce optically active steroid hormones. Long-term and large-scale production of steroid hormone preparations based on the Torgov reaction sequence and asymmetrization was organized by two companies at least, Schering AG in Germany and Akrihin in the U.S.S.R. It was a challenge to win the race for commercially viable syntheses of steroids. Even in hundreds years, chemists will know well his reaction. A number of giants of bioorganic chemistry had been working in that area with limited success. Since 1958, Torgov participated in all World Congresses on Chemistry of Natural Compounds. Nobel Laureate Sir D. Barton appreciated Professor Igor Torgov’s contribution to science and in 1966, he invited Professor Torgov on behalf of the Royal Chemical Society to present a lecture series in the United Kingdom. In addition, Torgov’s steroid total synthesis was highly regarded by Nobel Laureate Sir Alexander Todd.

Studying history, especially of the French Revolution and World Wars, was Igor Torgov’s favorite hobby. He appeared to have read all best books on these topics printed in Russian, English, French and German. With his brilliant memory he mastered all the important dates of world history. In one interview [1], when he who had out-lived many governments, was asked which historical time he would have liked to live, he has joked that he would prefer to live in the 19th century. He explained that no politicians or governors of the 19th century could have carried out the atrocities of the 20th century. He condemned the crimes of the Bolshevists until his death.

As an examiner and teacher of many generations of bioorganic chemists and biochemists at Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry of Russian Academy of Sciences in Moscow, Professor I. Torgov imparted to his students a taste for rigorous studies of chemical processes and their importance for the functioning of living cells. He was always benevolent, powerfully intelligent and anxious to help others. He never lost his boundless memory – he could recite hours of verse or recount the dates and chronicles of events of centuries and millennia past. Even at 92 years of age he effectively held sessions at the Scientific Council of the Institute of Bioorganic Chemistry and participated in sessions of the Russian Academy of Sciences, to which corresponding membership had been awarded him in 1972. All who knew him loved him. He is survived by two children and five grandchildren. With his death, the field of chemistry of natural compounds has lost one of its giants and the Russian Federation has lost one of its greatest sons – a patriot who remained devoted to his country throughout his long life, despite all the political storms of the 20th Century.

References


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