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Friedrich Asinger (1907–1999): A Mediator between Basic and Applied Research

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Friedrich Asinger, who conducted seminal work on the direct synthesis of sulfur and nitrogen heterocycles by the "*concomitant action of sulfur and ammonia on ketones*", was born on June 26, 1907 (Figure 1). His name reaction, the solvent-free, three-component, three-phase, one-pot reaction at room temperature is according to W. A. Pryor[1] "*the only known sulfur oxidation that has an appreciable rate at 25 °C.*" The reaction, discovered fortuitously by Asinger and which he first reported in 1956 at the chemists' congress in Salzburg,[2] is known today as the Asinger reaction.[3] It provided access to more than 20 new heterocyclic systems which were modified by a palette of follow-up reactions described in more than 120 publications and 60 patents.

Figure 1. Friedrich Asinger (1907–1999). Photograph from the year 1966.

Friedrich Asinger found international recognition not only on account of his heterocyclic syntheses but also in his role as an industrial organic chemist (at the Leuna-Werk of IG-Farben) and as a pioneer of petrochemistry. In addition to his remarkable industrial contributions on detergent-based materials (Mersolate) and plasticizers (Mersapone), it was in particular his fundamental work on the chlorination, sulfochlorination, sulfoxidation, and nitration of long-chain paraffins and on the reaction of long-chain monoolefins that received international recognition. The introduction of Mersolate, which was produced at 80000 t per year during World War II, marked the first synthetic route for detergent production.

The name Asinger became a synonym for teaching and research in petrochemistry, mainly thanks to his published standard works (*Chemie und Technologie der Paraffinkohlenwasserstoffe*, *Chemie und Technologie der Monoolefine*, *Einführung in die Petrolchemie*, *Die Petrolchemische Industrie I and II*).[4] It is not exaggerated to say that Asinger gave important stimulus to petrochemistry, indeed considerably helped shape the transition from the chemical raw material coal to natural gas and oil.

He also followed with concern the over-exploitation of the valuable raw materials oil and natural gas for energy production, and he became an advocate of atomic energy and coal chemistry. As early as the 1960s he advocated the use of methanol as an energy and chemical source for the future. In his book *Methanol: Chemie- und Energierohstoff*,[5] published in 1986—20 years before the currently much-discussed book *Beyond Oil and Gas* by G. A. Olah et al.[6]—Asinger pointed out routes to the chemical and energetic utilization of methanol: "*If hydrogen were cheaply available, this readily obtainable, pure, sulfur-free carbonic acid could serve as a starting material for methanol synthesis*" and "*If fossil raw material sources one day become increasingly short in supply and more expensive, or are even totally exhausted… there remains apart from biomass only carbonic acid as the source of raw material for the organic chemical industry!*"

Born in Freiland (Lower Austria), Asinger studied chemistry at the Technische Hochschule in Vienna and was granted his doctorate in 1932 for the dissertation "Über den Einfluss von Substituenten auf die Verseifungsgeschwindigkeit von Benzalchlorid" [The Effect of Substituents on the Rate of Hydrolysis of Benzalchloride]. For financial reasons he turned down offers for a Habilitation and for a postdoctorate with L. P. Hammett (1894–1987) at Columbia University. After positions in medium-sized chemical companies in Vienna, in 1937 he took up a position as research chemist at the Leuna-Werk, first as group leader, then later as head of research. Parallel to his industrial activities he received his Habilitation at the Technische Hochschule Graz (1943), and he was appointed honorary lecturer ("Honorardozent") at the Institut für Organische Chemie der Universität

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Halle-Wittenberg, then under the leadership of Karl Ziegler. In 1946, as part of Operation Ossawakim, the forced deportation of skilled workers and scientists from the Soviet Occupied Zone to the territory of the Soviet Union, he was transferred to the Soviet Union, where he was entrusted with research on rocket fuels.

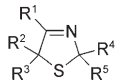
During his time in the Soviet Union he wrote the drafts of his above-mentioned textbooks and monographs on paraffins, monoolefins, and petrochemistry.[7] In 1954, after eight years and nine winters—as Asinger always put it—he returned home to the German Democratic Republic (GDR) from the Soviet Union, resumed work at the Leuna-Werk, and was soon appointed Professor for Organic Chemistry at the Universität Halle-Wittenberg. In 1958 he was appointed Ordinarius für Organische Chemie and Director of the Institut für Organische Chemie der Universität Dresden.

In 1959 he was offered the position of Ordinarius für Technische Chemie und Direktor des Instituts für Technische Chemie und Petrolchemie at the RWTH Aachen. He accepted the appointment, and as an Austrian citizen he was able to move to the Federal Republic of Germany; none of his German workers in the GDR were able to accompany him and in Aachen he had to build a completely new research group. He remained at Aachen until his retirement in 1972 and remained closely associated with the institute until his death in 1999. More than 150 chemists received their doctorates as "Asinger students", and more than one in ten took up university careers.

Friedrich Asinger experienced, lived through, and survived more than nine decades of the 20th century: the Hapsburg Monarchy and its demise, the fall of the First Republic in Austria and the Weimar Republic, the Nazi regime with the "Anschluss" of Austria, World War II, the frightful end with tremendous destruction, the Stalin era in the Soviet Union, communism in the GDR, and finally during the second half of his life the democracy and the freedom of the Federal Republic of Germany, the reunification of East and West Germany, and the end of the GDR and the Soviet Union. It is reported that as a 26-year-old Asinger became a member of the (forbidden) National Socialist Party (NSP) in Vienna but also belonged to the Vaterländischen Front (1934/35), closely aligned to the Christian Socialists.[8] One thing is certain: he was a member of the Nazi party during his industrial activities in Leuna, without apparently achieving any particular prominence.[9]

50 Years of the Asinger Reaction

In experiments on the production of rocket fuels during his forced stay in the Soviet Union Asinger studied the combined effect of elemental sulfur and gaseous ammonia on pentan-3-one and cyclohexanone at room temperature. In each case he obtained a homogeneous product in almost quantitative yield: a compound with a boiling point 96 °C (12 Torr) and a melting point of 81.5–82 °C. After his return to Halle the structure of the product which Asinger had brought from the Soviet Union—fused in vials—was rapidly elucidated. Asinger had discovered a simple route to the ring system of the 3-thiazolines **1** in a "three-component one-pot reaction".



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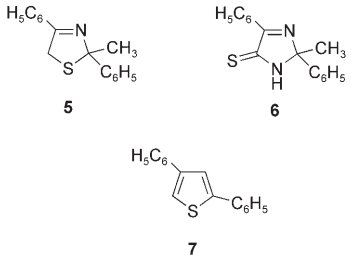
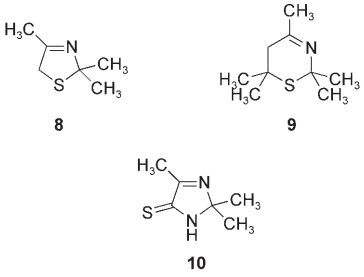
Until that time only one compound of this class had been described,[10] the presumed degradation product uscharidin of the Indian arrow poison uscharin. The 3-thiazolines are formed from a monothiolation in the α position to the keto group and subsequent α-aminoalkylation and ring closure with elimination of water. Asinger and co-workers later found that multiple thiolations are also possible. Thus ketones with α-CH_2 groups react astonishingly with ammonia and sulfur in methanol at −70 °C in the presence of piperidine to form sulfur-free substituted imidazoles, the formation of which results from an intermediate dithiolation. The corresponding reaction of pentane-3-one forms 5-methyl-2,2,4-triethyl-2*H*-imidazole (**3**) as the main product in 60% yield as well as 3-thiazoline **2** in only 5% yield and small amounts of 4-amino-3,5-dimethylisothiazole (**4**) (Scheme 1).

Ketones with an α-methyl group (acetophenone, acetone, etc.) are a special case. The Asinger reaction of acetophenone under standard conditions yields in addition to a small amount of 3-thiazoline **5**, a yellow crystalline compound, 2-methyl-2,4-diphenyl-3-imidazoline-5-thione (**6**). Under optimized conditions both compounds can be obtained in good to very good yields, and the thiophene **7** may also be obtained in moderate yield under special conditions.



5 **6** **7**

As early as 1842 Zeise[11] had treated acetone with sulfur and ammonia without, however, being able to isolate identifiable products (lecture given at the Conference of Scandinavian Natural Scientists 1842). In initial experiments (1957) the Asinger reaction with acetone (room temperature, solvent-free) provided the expected 3-thiazoline **8**, although in only 8% yield together with 2,2,4,6,6-pentamethyl-1,3-dihydrothiazine (**9**) (6%). Under the same conditions under which the sulfur-free dithiolation product 2*H*-imidazole structure **3** was formed from pentane-3-one, acetone formed 2,2,4-trimethyl-3-imidazoline-5-thione (**10**) in good yield (> 70%) as a result of a trithiolation.



8 **9** **10**

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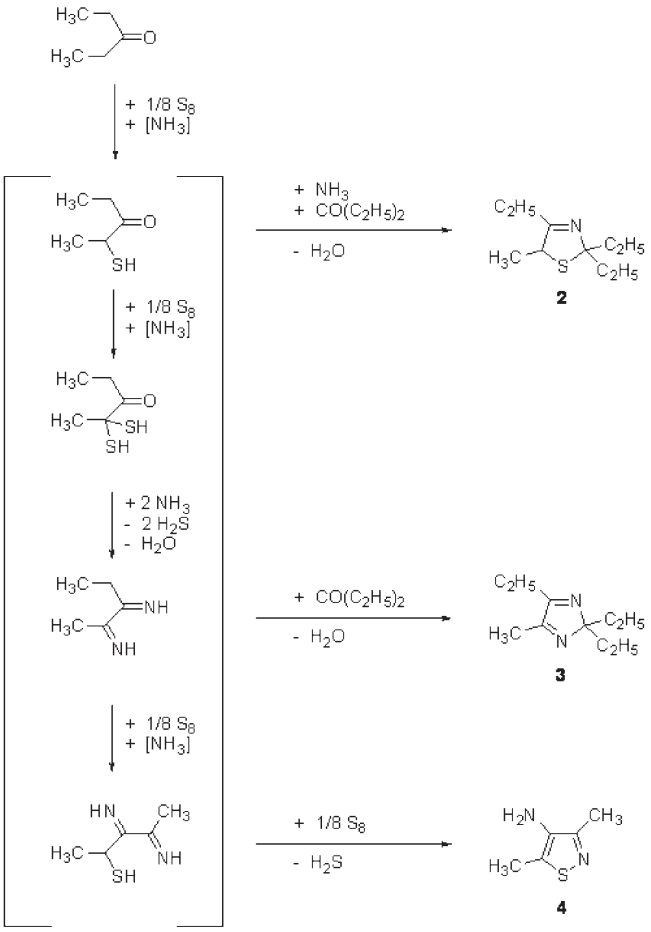
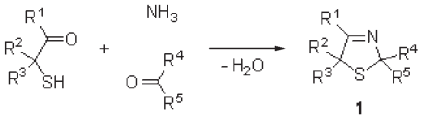


Scheme 1. Asinger reaction of pentane-3-one: mono-, di-, and trithiolation.

Many ketones with α-methyl, methylene, or methine groups can be used as substrates in the Asinger reaction. Structurally isomeric 3-thiazolines are formed if unsymmetrical ketones with at least one thiolatable H atom in each of the two α positions are used.

However, the direct synthesis of thiazolines has its limits. Cyclopentanone reacts very indistinctly, as do aldehydes. One exception is isobutyraldehyde, which reacts very smoothly with sulfur and ammonia to give 2-isopropyl-5,5-dimethyl-3-thiazoline, the starting material for the Asinger synthesis of D-penicillamine, in very good yields.

Considerable flexibility with respect to the choice of substituents on the thiazoline ring is seen in the "resynthesis", also discovered by Asinger, that is, the reaction of α-sulfanylketones or aldehydes, which can be obtained from α-halocarbonyl compounds or by hydroysis of 3-thiazolines, with ammonia and an oxo component (Scheme 2).



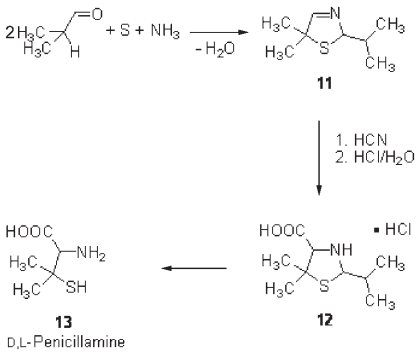
Scheme 2. Access to 3-thiazolines by resynthesis.

There are a number of cross-relationships between the Asinger reaction and the results of other research groups. One interesting variant is the Gewald reaction,[12] the reaction of a carbonyl compound having an α-methylene group with elemental sulfur and a α-cyano ester to furnish the corresponding 2-aminothiophenes.

Special 3-thiazolines and the 4-acyl-4-thiazolines readily obtained from them by reaction with acetic anhydride were used by R. B. Woodward and H. Vorbrüggen[13] as building blocks in the total synthesis of cephalosporin. Thiazolidine-4-phosphonic acids were prepared by the research group of J. Martens by the asymmetric catalytic hydrophosphonolation of prochiral 3-thiazolines (azomethine group!) with chiral lanthanoid compounds, and were hydrolyzed with retention of configuration to provide α-amino-β-thiophosphonic acids.[14] The research group also succeeded in synthesizing 3-thiazolines with a stereocenter at the C2 atom as well as subsequent stereospecific reactions.[15] A remarkable seven-component one-pot reaction was discovered as a combination of the Asinger reaction with the Ugi reaction.[16] The 3-thiazoline obtained by the four-component reaction of α-bromoacetaldehyde, NaSH, ammonia, and a further oxo component reacts with carbon dioxide, methanol, and isonitrile to give the corresponding substituted thiazolidines.

Penicillamine Synthesis: The Asinger Process

The most remarkable application of the Asinger reaction is the synthesis of D-penicillamine (Asinger process; Scheme 3).[17] The reaction of isobutyraldehyde with sulfur and ammonia provides the 3-thiazoline **11** in high yield. The addition of anhydrous hydrogen cyanide to the azomethine group and subsequent acid hydrolysis results in 2-isopropyl-5,5-dimethylthiazolidine-4-carboxylic acid (**12**), which has two stereocenters. Water-vapor hydrolysis gives the D,L-penicillamine (**13**), which is treated with acetone to provide the so-called "acetone adduct", 2,2,5,5,-tetramethylthiazolidine-4-carboxylic acid (only one asymmetric center!). After



Scheme 3. Asinger process for the preparation of penicillamine.

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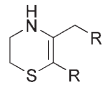
formylation the racemate is cleaved with the aid of optically active bases (L-lysine, (−)-norephedrine, (−)-pseudonorephedrine). The hydrolysis of the D isomer yields pure D-penicillamine. The "incorrect" isomer is re-racemized and recycled. Fully synthetic D-penicillamine was introduced to the market by Bayer and the Degussa pharmaceuticals division under the name Trolovol as a therapeutic against rheumatoid arthritis and Wilson's disease and as an antidote to heavy-metal poisoning. The Asinger process is still used today on an industrial scale.

The Asinger Reaction with Ethylene Imine

The reaction of certain ketones such as pentane-3-one with elemental sulfur and ethylene imine at room temperature affords 5,6-dihydro-1,4-thiazines (**14**) in



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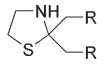

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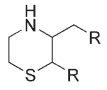

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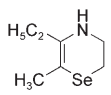
high yields. 2,2-Disubstituted thiazolidines **15** are formed as by-products. As enamines, the dihydrothiazines can be hydrogenated with formic acid to furnish thiomorpholines **16**. A resynthesis (reaction of α-sulfanylcarbonyl compounds with ethylene imine) is also possible.

Whereas all attempts to prepare selenium analogues of the 3-thiazolines or imidazoline-5-thiones by reaction of elemental selenium and gaseous ammonia were unsuccessful, it was surprisingly straightforward to prepare the corresponding 5,6-dihydro-1,4-selenazine **17** in about 50% yield by the combined action of elemental selenium and ethylene imine on pentane-3-one. Reaction with formic acid provides access to selenomorpholines such as **18**.



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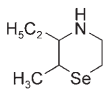

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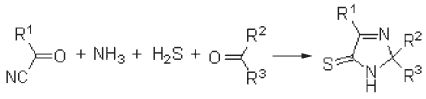
Asinger and co-workers were also the first to succeed in preparing unsubstituted and monosubstituted α-oxothiamides from acylnitriles and hydrogen sulfide, or from certain ω,ω-dichloromethylketones (acetophenone, pincoline), primary amines, and sulfur in order to obtain substituted imidazolines or imidazoles. α-Oxothioamides react with ammonia and ketones to form imidazoline-5-thiones **19**. 3-Imidazoline-5-thiones can also be prepared in a four-component one-pot reaction from acylnitriles, hydrogen sulfide, ammonia, and ketones (Scheme 4).



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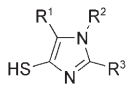
Scheme 4. Four-component one-pot method for the synthesis of substituted 3-imidazoline-5-thiones **19**.

Other Reactions

The reaction of unsubstituted or monosubstituted α-oxothiamides with Schiff's bases afford 4-sulfanylimidazoles **20** (highly exothermic reaction) or imidazolium-4-thiolates **21**.



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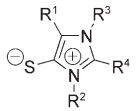

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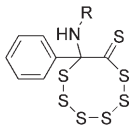
Novel sulfur-rich thiocanes, which Asinger assigned the 8-alkylamino-8-phenyl-7-thioxo-1,2,3,4,5,6-hexathiocane structure **22** on the basis of degradation reactions and spectroscopic data, are obtained by reaction of methyl aryl ketones such as acetophenone with large excesses of both elemental sulfur and primary amines. However, the work of H. Matschiner[18] (X-ray crystal structure analysis) supports the 8-alkylamino-8-phenylmethylidene-1,2,3,4,5,6,7-heptathiocane structure **23**.



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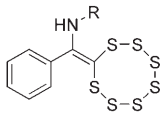

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