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Disappearing Polymorphs Revisited

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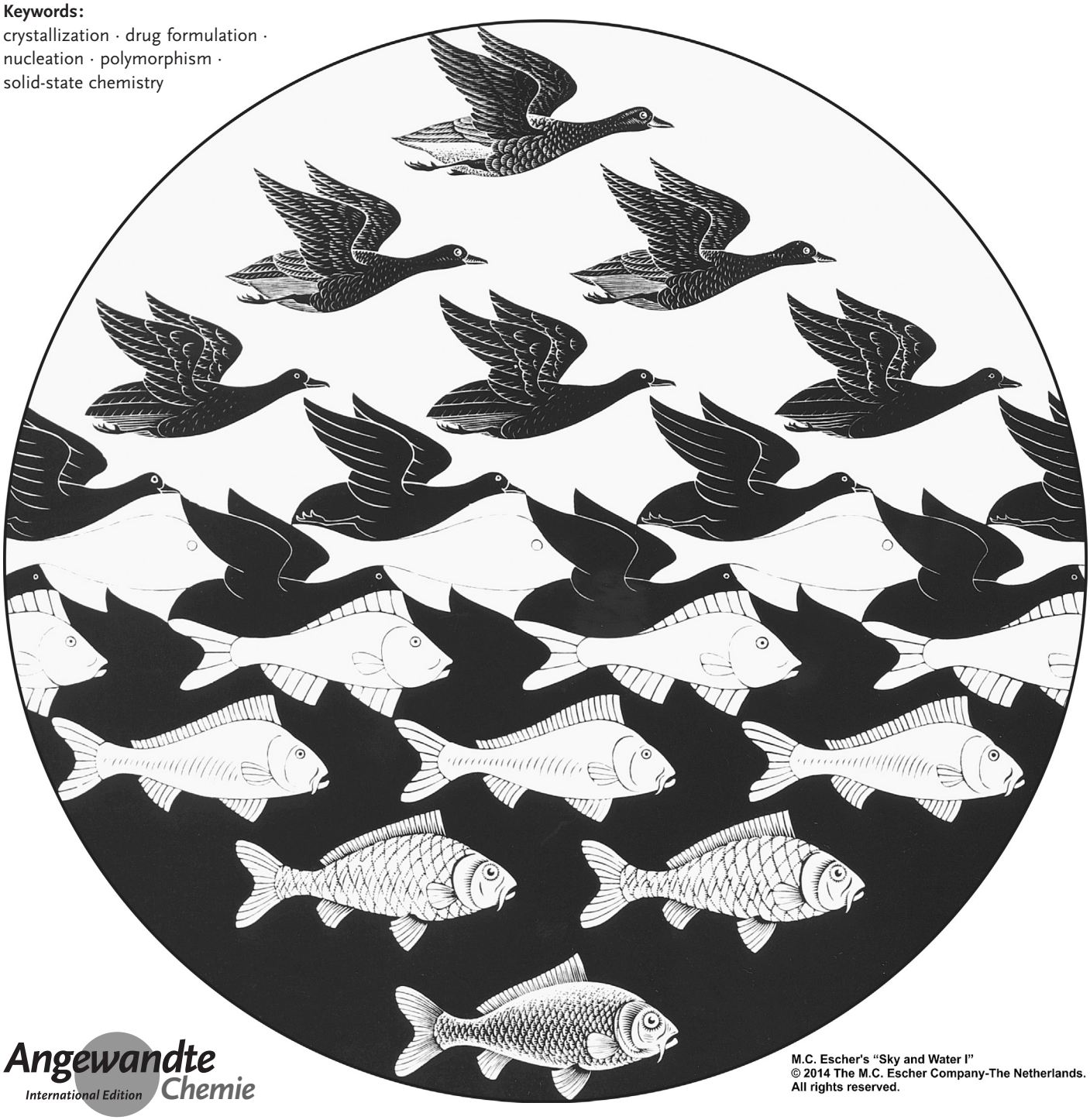

M.C. Escher's "Sky and Water I"

Nearly twenty years ago, Dunitz and Bernstein described a selection of intriguing cases of polymorphs that disappear. The inability to obtain a crystal form that has previously been prepared is indeed a frustrating and potentially serious problem for solid-state scientists. This Review discusses recent occurrences and examples of disappearing polymorphs (as well as the emergence of elusive crystal forms) to demonstrate the enduring relevance of this troublesome, but always captivating, phenomenon in solid-state research. A number of these instances have been central issues in patent litigations. This Review, therefore, also highlights the complex relationship between crystal chemistry and the law.

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1. Introduction

There is a continual and increasing demand for crystalline molecular materials with specific, fit-for-purpose physicochemical properties.[1–6] Interest in polymorphism, crystallization, and (in industry) in robust process development has surged over the last two decades,[7,8] as evidenced by the immense growth in knowledge concerning the design, preparation, and characterization of crystalline materials.[9] This expanding interest and demand for promising materials drives investigations of the solid form (i.e. polymorphs, solvates, hydrates, and amorphous materials) landscapes[8,10] of potentially relevant compounds, with the goal of identifying the optimally performing solid among them.

A broad range of crystallization techniques is generally employed to search for the most stable crystal form in hundreds or (in some cases) thousands of experimental attempts.[11] New crystal forms can, however, emerge unexpectedly long after the carefully designed and executed screening experiments are completed. Such a sudden emergence of a new crystal form can be unsettling and problematic, especially in the late stages of a product development or even following launch, because the newly emerged form can exhibit different (possibly undesired) properties. Equally disruptive is the emergence of a thermodynamically more-stable crystal form, in accord with Ostwald's Rule of Stages,[12] concurrent with the disappearance of the less-stable known forms that signal a loss of control of the production process. While it may create roadblocks in the development process or even the marketed product of the solid form of a compound of interest, the consequences of the appearance of a new form are not necessarily negative. The serendipitous appearance of a new form may provide a substance with improved characteristics.

Unfortunately, our current understanding of the mechanisms and processes involved in the nucleation and growth of crystals is still insufficient for precise control over the formation or disappearance of a polymorph (or any other crystal form).[13,14] Nearly twenty years ago, Dunitz and Bernstein presented an overview of the disappearing polymorph phenomenon[15] that has captivated and intrigued solid-state scientists since. In their review, Dunitz and Bernstein voiced their belief that crystal forms do not disappear permanently; on the contrary, once a solid form has been obtained, in principle it can always be reproduced if the right experimental conditions are met.[15–18] In the same spirit as the earlier survey, this Review aims to discuss selected recent occurrences of disappearing polymorphs and of elusive crystal forms that have not only triggered the curiosity of researchers, but have also affected the business of pharmaceutical and health care companies. These examples illustrate how apparently stable polymorphs can suddenly disappear, and how elusive crystal forms can be prepared given the availability of conditions specifically designed to promote their formation. The uncontrolled loss of a crystal form can have serious consequences, and there is thus an urgent need to develop methods that provide absolute control over crystal nucleation and growth,[13,14] which is still an art, rather than a routine procedure.[19]

In addition to citing examples of disappearing polymorphs from the literature and our own laboratories, the 1995 review dealt with a number of issues that are still the subjects of debate. There have also been a number of patent litigations in which the same issues have arisen and have been interpreted

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variously by the courts. We will deal initially with those aspects of the subject and follow with the descriptions of a number of recent cases of disappearing polymorphs (and other crystal forms), as well as further details on some of those previously cited.

2. Disappearing Polymorphs—The Concept and Misconceptions

One of us (J.B.) recently recounted the genesis of the 1995 review,[20] which was based on earlier cases in the laboratories of both Bernstein and Dunitz as well as additional examples we had encountered in the course of our involvement in the ranitidine hydrochloride litigations. In the twenty-year interim we have experienced numerous additional examples in which the phenomena described therein were either misinterpreted or misunderstood. Hence, we review some of those here.

2.1. The Concept

As we described in the section of the 1995 review headed "Vanishing Polymorphs", a disappearing polymorph refers to a crystal form that has been prepared at least once and whose existence has been established experimentally by some observation or measurement. Subsequent attempts to prepare the same crystal form by the same procedure lead to a different crystal form, alone or together with the old one. If a mixture appears in the first instance, then very often in subsequent preparations the new form dominates and the old form is no longer obtained.

The phase rule limits to one the number of stable crystal forms that may exist under a specific set of conditions. The old—"disappeared"—form is generally less stable than the new one under those specific conditions. In thermodynamic terms, it is metastable, although that does not necessarily imply that it would spontaneously convert into a more stable form; it only means that it is at a higher energy minimum than the most stable state. To invoke a familiar example: diamond is metastable with respect to graphite; nevertheless, as is widely advertised, "diamonds are forever".

The fact that a crystal form once existed, but is now difficult to prepare by the same method that was previously used, does not mean that it is impossible to prepare again. It has not been relegated to the "crystal form cemetery".[21] Every crystallization is a competition between kinetic and thermodynamic factors. As noted in the last sentence of the 1995 review, "*it is* always *possible to obtain [the old form] again; it is only a matter of finding the right experimental conditions*"—thermodynamic and kinetic.

Recovering a crystal form that has disappeared may require considerable time and effort and invoke some inventive and creative chemistry. The examples given below will demonstrate the kinds of strategies that have been employed to recover crystal forms that have disappeared.

2.2. Seeds and Seeding

The 1995 review also contains a section headed "Seeding". Intentional seeding is a well-known technique for inducing crystallization and is widely used, especially in the pharmaceutical industry. Unintentional seeding arises from the presence of small amounts—indeed, in principle one particle is sufficient—of the solid material that is present even as a contaminant. As we noted earlier, "*Unintentional seeding is often invoked as an explanation of phenomena which are otherwise difficult to interpret. We shall argue in favor of this explanation, although there is no consensus about the size and range of activity of such seeds, which have never actually been directly observed.*"[15]

The situation this statement describes has led to considerable controversy, particularly in the framework of patent litigations involving crystal forms. That controversy very much represents the clash between the cultures of science and the law, and in light of that controversy it seems appropriate, indeed compelling, to put the phenomenon of unintentional seeding into a proper scientific perspective in this Review.

Virtually every chemist has at some time attempted to crystallize a compound. Crystallization is perhaps the classic method of purification, and the technique is one of the first mentioned in purification methods in any undergraduate organic chemistry laboratory textbook. Practicing chemists soon learn, often simply by experience, that it is frequently very difficult to crystallize a newly synthesized substance,

Krešo Bučar obtained a BSc in chemistry with Dr. Ernest Meštrović at the University of Zagreb, and a PhD in chemistry from the University of Iowa with Prof. Leonard R. MacGillivray. He then started his independent research career as a Royal Society Newton International Fellow at the University of Cambridge with Prof. William Jones. While in Cambridge, he was also a Bye-Fellow at Sidney Sussex College. He recently joined the Department of Chemistry at University College London as UCL Excellence Fellow. His research interests mainly concern molecular cocrystals and their applications.

Robert Lancaster joined Glaxo in 1969, studied part-time to obtain a Grad RIC degree. He gained exposure to the phenomenon of polymorphism in the mid-70s and completed his PhD at the University of East Anglia in 1986. He worked closely with process and pharmaceutical development scientists, specifically looking at issues surrounding all aspects of crystallization and polymorphism. He had some exposure to legal aspects of two high profile Glaxo (GSK) drugs. After retiring from GSK, he joined Prof. Sally Price's group at University College London on a part-time basis.

while subsequent crystallizations are considerably more facile. The situation was documented over half a century ago by Wiberg in his classic text "Laboratory Technique in Organic Chemistry" in the section entitled "Inducing Crystallization": "*When a compound is prepared for the first time in a laboratory, it is often observed that it is relatively difficult to effect crystallization. However, once the compound has been obtained in the crystalline state, it is usually easy to effect crystallization, and it has been suggested that after initial crystallization crystal nuclei are present in the laboratory and induce crystallization*".[22] In the current context those nuclei are unintentional seeds.

Many laymen are initially skeptical about a phenomenon caused by particles that cannot be seen, although very few would accept an invitation for a casual—and unprotected—visit to the pneumonia ward at their local hospital. The approximate limit of visual detection for the naked eye is a crystal that weighs approximately 10^{-6} g. We pointed out earlier that a speck of that size contains approximately 10^{16} molecules and while there are various estimates of the size of a critical nucleus that could act as a seed even the largest—a few million molecules[23]—would mean that an invisible particle could contain up to 10^{10} of such unintentional seeds.

Where do these microscopic particles come from? As noted elsewhere, depending on our location, the air contains a vast number of submicroscopic particles. For a normal urban environment there are approximately 10^6 airborne particles of 0.5 micrometer diameter or larger per cubic foot, the number being reduced by an order of magnitude in an uninhabited rural environment. A sitting individual generates roughly one million dust particles ($\geq$0.3 micrometer diameter) per minute (a visible particle is usually $\geq$10 micrometers).[24] Clean rooms for various purposes (e.g. surgery, biological or pharmaceutical preparations, semiconductor fabrication) employ very sophisticated technology to remove these particles and to prevent subsequent contamination. Therefore, the possible presence of seeds of a newly formed polymorph in a laboratory, a manufacturing facility, or any location having been exposed to that form cannot be casually dismissed; indeed its presence would be hard to avoid. In his comprehensive monograph on crystallization, Mullin notes that, "*Atmospheric dust frequently contains particles of the crystalline product itself, especially in industrial plants or in laboratories where quantities of the material have been handled…Once a certain crystalline form has been prepared in a laboratory or plant, the working atmosphere inevitably becomes contaminated with seeds of the particular material.*"[23]

So much for the atmosphere. What about the crystallizing medium, usually a solution? The normal determination that dissolution has been completed is made by visual inspection. If the solution is clear to the human eye all the solute is assumed to be in solution. Mullin has also pointed out that *"aqueous solutions as normally prepared in the laboratory may contain $>10^6$ solid particles per cm^3…"*.[23] These can be impurities or particles of the solute that have not undergone complete dissolution, and can serve as seeds for the subsequent crystallization.

The presence and influence of microscopic seeds and their influence on crystallization is thus well established. Nevertheless, it is difficult for many who lack practical laboratory experience to accept their existence. In the history of chemistry there have been many instances of inductive reasoning in understanding chemical phenomena. The existence of atoms was proposed and accepted for nearly two hundred years before an atom was actually "seen". Yet no chemist doubts the existence of atoms or the ability to make and break bonds between them.

The presence and influence of seeds may be invoked to explain the disappearance of one crystal form at the expense of a new form. In such a case, the unintentional seeding by the new form may be quite aggressive, preventing the crystallization of the old form. However, there is no intrinsic reason why every system is influenced by such aggressive unintentional seeding. There are many known examples of multicrystalline materials in which the various forms can be prepared and maintained in the known presence of other forms. As for polymorphism in general, **every system is unique** and must be individually studied and characterized to understand how to prepare and characterize each form.

2.3. "Universal Seeding"

The publicity surrounding some cases of aggressive unintentional seeding led to discussions, particularly in legal circles, of the alleged phenomenon of universal seeding—that is, in some cases of disappearing polymorphs, when the old form could not be made by the old process somehow, there was an implication that the entire universe must be seeded. To put the matter to rest it is important to quote a footnote from the 1995 review: "*The claim for 'universal seeding', taken literally, is obviously absurd. After all, the universe is estimated to contain about a millimole of stars, so one seed per star (per solar system)—not much—would need about 100 kg of the compound in question ($M_r \approx 100$)*".

A number of cases of aggressive seeding have attained considerable notoriety, and these will be described below. In instances where various locations at considerable distance have become "infected" with a new form within a relatively short time, it has been possible to trace the source of the seeding in successively affected locations.

Joel Bernstein studied chemistry at Cornell University (BA 1962) and Yale University (PhD 1967). He was then a postdoctoral fellow with Ken Trueblood at UCLA and then with Gerhardt Schmidt at the Weizmann Institute. He is professor emeritus at Ben-Gurion University of the Negev in Israel, which he joined in 1971 and from which he retired in 2010 as the Barry and Carol Kaye Professor of Applied Science. He is currently Global Distinguished Professor of Chemistry at New York University having taught at Abu Dhabi and Shanghai. His research interests concern chemistry of the organic solid state, particularly polymorphism.

3. Recent Instances of Disappearing Polymorphs and Elusive Crystal Forms

This section describes several of the most (in)famous recent cases of disappearing polymorphs and other crystal forms. In addition, in relation to the sudden and unexpected disappearance of a well-known crystal form, we consider it particularly relevant to describe cases where elusive crystal forms, believed to be non-existent, were prepared.

3.1. Ranitidine Hydrochloride

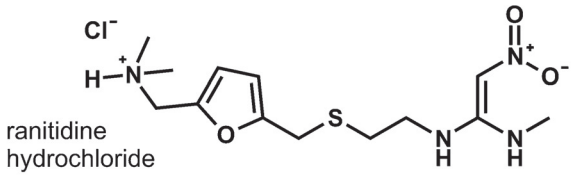
In the early 1970s, James Black at (then) Smith, Kline & French identified the histamine type 2 (H_2) receptor and from the preparation of a series of H_2-receptor antagonists developed the first antiulcer drug, cimetidine (Tagamet®), for which he won the 1988 Nobel Prize in Medicine. H_2-receptor antagonists are among the miracle drugs of the 20th century. Prior to their introduction (and the subsequent entry of proton pumps) there were millions of sufferers of peptic ulcers worldwide with a significant number of fatalities; since their introduction, the surgical procedure for removing peptic ulcers has essentially been eliminated from the modern medical school curriculum.

The dramatic success of cimetidine led to industry-wide efforts to develop additional H_2-receptor antagonists. In 1977, Allen & Hanbury (then a part of Glaxo Group Research, now GSK) developed ranitidine and its hydrochloride (Figure 1 a), for which a US patent was issued in 1978.[25] The preparation of the hydrochloride following the multistep synthesis of ranitidine base is given in "Example 32" of the patent (Figure 1 b).

Subsequent development of the drug over nearly four years involved batch scale-ups to a multi-kilogram scale in the company's pilot plant by employing essentially the chemistry described in Example 32.[10] The batch prepared on April 15, 1980 failed the quality control IR analysis, which exhibited a hitherto unobserved sharp peak at 1045 cm^{-1}, and suggested the formation of a new crystal form designated **Form 2**. The subsequent four batches exhibited increasing amounts of **Form 2** and the same process no longer produced the (now designated) **Form 1**. Considerable efforts to revert to the production of **Form 1** by essentially the same process were unsuccessful. Thus, this is clearly a case of a disappearing polymorph. Serendipitously, **Form 2** had considerably improved filtering and drying characteristics which, in addition to the novelty of the new polymorph, formed the basis for a patent application, granted in 1985.[10] The crystal structures of both forms have been subsequently determined; both forms crystallize in the monoclinic $P2_1/n$, space group, wherein the nitroethenediamine moiety of the ranitidine cations displays different conformations and degrees of disorder (Figure 1 c).[26–28] This is thus also an example of *conformational polymorphism*.[29]

Glaxo launched ranitidine hydrochloride in 1984 as Zantac™ and by 1992 it was the world's best-selling drug at US$ 3.44 billion per year, when sales for the next largest drug (Bayer's Adalat Procardia™) were about half that amount.[30]

a)



ranitidine hydrochloride

b)

EXAMPLE 32

N-[2-[[[5-(Dimethylamino)methyl-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine hydrochloride

N-[2-[[[5-(Dimethylamino)methyl-2-furanyl]methyl]-thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine (50 g, 0.16 mole) was dissolved in industrial methylated spirit 74° o.p. (200 ml) containing 0.16 of an equivalent of hydrogen chloride. Ethyl acetate (200 ml) was added slowly to the solution. The hydrochloride crystallised and was filtered off, washed with a mixture of industrial methylated spirit 74° o.p. (50 ml) and ethyl acetate (50 ml) and was dried at 50°. The product (50 g) was obtained as an off-white solid m.p. 133°–134°.

c)

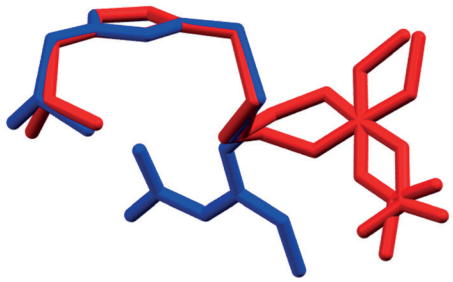


Figure 1. a) Molecular structure of ranitidine hydrochloride. b) Example 32 from patent US 4128658A ("Aminoalkyl furan derivatives"), the apparently straightforward procedure for the preparation of **Form 1** of ranitidine hydrochloride. c) Overlay of the ranitidine cation from **Form 1** (blue) and **Form 2** (red). **Form 2** features a disordered nitroethenediamine moiety.

In accord with the terms of the 1984 Hatch–Waxman Act in the US, by 1990 a number of generic drug companies were planning to enter the market with **Form 1** in anticipation of the 1995 expiration of the **Form 1** patent. Attempts to make **Form 1** were based on carrying out Example 32. As transpired in the course of the subsequent litigations, essentially all of those attempts started with commercial **Form 2**; hence, at the very least **Form 2**—thus seeds of **Form 2**—were present in the environment in which attempts to follow Example 32 were being carried out.

Following numerous attempts to prepare **Form 1** according to Example 32, which led almost exclusively to **Form 2**, the Canadian generic firm Novopharm claimed that Glaxo had never made **Form 1** and sought approval from the Food and Drug Administration (FDA) to market **Form 2**. Glaxo aimed to prevent Novopharm (and others) from entering the market with **Form 2** by suing them for the infringement (actually, virtual infringement under the Hatch–Waxman Act) of their **Form 2** patent. Novopharm admitted infringement of **Form 2**, but argued that the **Form 2** patent was inherently anticipated in the **Form 1** patent, since their attempts to prepare **Form 1** according to Example 32 led to

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