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Drying of Organic Solvents: Quantitative Evaluation of the Efficiency of Several Desiccants

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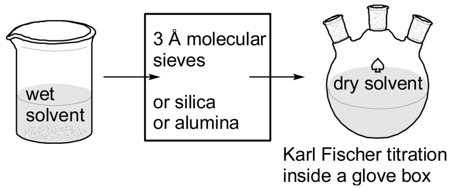

Various commonly used organic solvents were dried with several different drying agents. A glovebox-bound coulometric Karl Fischer apparatus with a two-compartment measuring cell was used to determine the efficiency of the drying process. Recommendations are made relating to optimum drying agents/conditions that can be used to rapidly and reliably generate solvents with low residual water content by means of commonly available materials found in most synthesis laboratories. The practical method provides for safer handling and drying of solvents than methods calling for the use of reactive metals, metal hydrides, or solvent distillation.

Introduction

Laboratories involved with synthesis require efficient methods with which to dry organic solvents. Typically, prescribed methods[1] are taken from the literature where little or no quantitative analysis accompanies the recommended drying method. Frequently, such methods call for the use of highly reactive metals (such as sodium) or metal hydrides, which increases the risk of fires or explosions in the laboratory. This situation is aggravated by hot solvents that are present during the distillation process that removes the solvent from the desiccant. While many laboratories employ relatively expensive commercially available drying trains that use filled cartridges to dry solvents (these systems appear to be largely based on the pioneering work of Grubbs[2] in this context), a large number of laboratories do not have access to such facilities. Accordingly, users of the published drying methods rely upon procedures that generally have little or no quantified basis of application and generate samples of unknown water content. In a rather elegant exception, Burfield and coworkers published a series of papers[3] some three decades ago in which the efficacy of several drying agents was investigated making use of tritiated water-doped solvents. The drying process was followed by scintillation readings, and several shortcomings were noted in "standard" drying practices. Despite this rather extensive analysis, many of the methods identified as inept are still in use today.

In altogether a different context, we required solvents that were reliably dried to levels of water in the sub-10 ppm range in order to test some principles of Lewis acid catalysis.[4] Since even the notable work of Burfield did not give the information needed to prepare super dry solvents required for our earlier study, we investigated the drying of several solvents as followed by coulometric Karl Fischer titrations. The titrator instrument was housed inside a glovebox for ultimate analytical sensitivity and instrument stability. While several other methods[3,5]

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have been developed for water determination in solvents, advances to the design and sensitivity of particularly coulometric Karl Fischer titrators since Burfield's day now allow accurate measurements of water in organic solvents at the ppm level.[6] The objective of the present study was not to comprehensively cover a wide cross section of drying agents (Burfield and co-workers have already adequately performed this task, highlighting problem areas in the process, particularly in their seminal paper on the topic[3b]) but to generate sufficient data to allow a practical, safe, and easy-to-reproduce approach to drying several common solvents to be recommended for everyday use.

Results and Discussion

For this study, tetrahydrofuran (THF), toluene, dichloromethane (DCM), acetonitrile, methanol, and ethanol were employed. Initially, the water content of the "wet" solvents (i.e., as obtained from commercial sources as analytical reagent-grade or HPLC-grade solvents) was measured. Accordingly, samples of about 3.0 mL (the exact amount added was accurately determined by weighing the filled syringe on a three decimal balance inside the glovebox and also the empty syringe after injecting the sample into the cell and calculating the difference) were injected into the anode compartment of the measuring cell of the Karl Fischer apparatus ($n = 6$ per sample). Where moisture content was very low for acetonitrile (see below, Table 4), larger sample sizes (of 10.0 mL) were employed as a countercheck to ensure accuracy. However, this approach results in very inefficient use of the Hydranal solution used for the Karl Fischer titration and also of rapid filling of the anode compartment of the measuring cell. It was therefore not followed as a matter of course since the accuracy was found to be the same for the different sample sizes. Samples of solvents removed directly from the bottles as received were analyzed: these data are used as a measure against which to judge the success of a given drying agent for a selected solvent. When the solvents were dried, drying was performed in triplicate. Each dried sample was analyzed six times to provide statistically acceptable precision data.

Tetrahydrofuran

THF is one of the mainstay solvents in synthesis laboratories. It is often predried over KOH pellets after which it is dried by heating under reflux over sodium wire in the presence of benzophenone as indicator.[1] Under these conditions, THF was found to be dried to approximately 43 ppm water content (Table 1). Matters significantly improve by simply allowing the solvent to stand over activated 3 Å molecular sieves (Table 1). Here, a 20% mass/volume (m/v) loading of the desiccant allows low ppm levels to be achieved after 48 h. Lower mass loadings also give good results but take significantly longer (about 5 days) to achieve single digit ppm levels of residual moisture. Several types of silica were assessed for their desiccating ability, including standard silica (70−230 mesh) typically employed in gravity column chromatography. Silica of some description is readily available in most synthesis laboratories making it an obvious target as a desiccant. There was essentially no correlation between pore size and drying efficiency with the various silicas used. A much stronger linear correlation was noted in respect of particle size, with finer particles given superior drying efficiencies in a given period of time (Figure 1; single passage of the solvent over a column of the silica, 10% m/v). While silica was reasonably good as a desiccant, neutral alumina was much better, rivaling the ultimate efficiency of molecular sieves after a single pass of the THF over a column of the activated alumina. For rapid drying, neutral alumina is the drying agent of choice, followed by storage over 3 Å molecular sieves if storage is necessary. Otherwise, simple storage over 3 Å molecular sieves provides THF with very low water content within 48−72 h. While THF may be polymerized to some extent upon standing with strongly Lewis/Brønsted acidic materials, this was not found to be problematic in the present instance given the short residence time of the THF on the alumina: samples of THF that had been passed over the alumina were evaporated to dryness with no significant residue remaining.

TABLE 1. Water Content in THF after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, "wet" solvent		107.8 ± 0.7
sodium/benzophenone[b]	48	43.4 ± 0.7
3 Å molecular sieves (10% m/v)	24	27.7 ± 1.0
3 Å molecular sieves (20% m/v)	24	14.7 ± 0.3
3 Å molecular sieves (20% m/v)	48	6.1 ± 0.2
3 Å molecular sieves (20% m/v)	72	4.1 ± 0.1
silica (28−200 mesh)[c,d]	*c*	56.2 ± 2.5
silica (35−60 mesh)[c,e]	*c*	105.7 ± 3.5
silica (60−100 mesh)[c,e]	*c*	89.4 ± 2.8
silica (70−230 mesh)[c,e]	*c*	82.5 ± 1.2
silica (100−200 mesh)[c,e]	*c*	74.6 ± 2.9
silica (200−425 mesh)[c,e]	*c*	59.5 ± 3.7
silica (100−200 mesh)[c,f]	*c*	69.0 ± 3.3
silica (200−425 mesh)[c,f]	*c*	60.8 ± 1.9
neutral alumina[c]	*c*	5.9 ± 0.4

[a] Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b] THF was distilled from the desiccant once the indicator had turned a persistent blue color. [c] Solvent was passed over a column of the desiccant, 10% m/v, inside the glovebox. The system was not assessed for "breakthrough" of water, i.e., to establish the capacity of the desiccant. [d] Silica (pore size 22 Å). [e] Silica (pore size 60 Å). [f] Silica (pore size 100 Å).

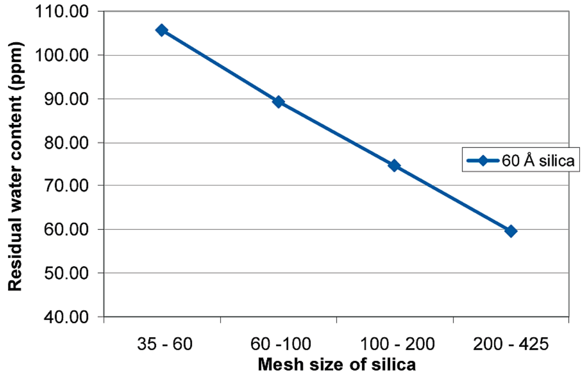

FIGURE 1. Linear dependency of the drying efficiency by columns of 60 Å silica (10% m/v) of THF with respect to silica particle size (data taken from Table 1).

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TABLE 2. Water Content in Toluene after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, "wet" solvent		224.9 ± 1.3
Sodium/benzophenone[b]	48	31.4 ± 1.9
3 Å molecular sieves (10% m/v)	24	0.9 ± 0.3
silica (10% m/v)[c]	*c*	2.1 ± 0.2

[a] Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b] Toluene was distilled from the desiccant once the indicator had turned a persistent blue color. [c] Solvent was passed over a column of silica (pore size 22 Å, 28−200 mesh) inside the glovebox. The system was not assessed for "breakthrough" of water, i.e., to establish the capacity of the desiccant.

TABLE 3. Water Content in DCM after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, "wet" solvent		22.4 ± 1.2
CaH_2[b]	24	12.9 ± 1.3
3 Å molecular sieves (10% m/v)	24	0.1 ± 0.1
silica (10% m/v)[c]	*c*	1.3 ± 0.3

[a] Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b] Dichloromethane was distilled from the desiccant. [c] Solvent was passed over a column of silica (pore size 22 Å, 28−200 mesh) inside the glovebox. The system was not assessed for "breakthrough" of water, i.e., to establish the capacity of the desiccant.

TABLE 4. Water Content in Acetonitrile after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, "wet" solvent		142.0 ± 1.2
3 Å molecular sieves (5% m/v)	24	4.0 ± 0.7
	48	1.8 ± 0.5
	72	< dl[b,c]
3 Å molecular sieves (10% m/v)	24	0.5 ± 0.4 (0.7 ± 0.1)[d]
	48	< dl[b,c]
activated neutral alumina (10% m/v)[e]	—[e]	5.9 ± 0.4

[a] Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b] For 2.6 and 8.7 g sample sizes (3.0 and 10.0 mL). [c] < dl = below detection limit of the Karl Fischer instrument. [d] 10.0 mL sample sizes (instead of the customary 3.0 mL) of the solvent gave the results in parentheses. [e] Solvent was passed over a column of alumina inside the glovebox. The system was not assessed for "breakthrough" of water, i.e., to establish the capacity of the desiccant.

TABLE 5. Water Content in Methanol after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, "wet" solvent		175.1 ± 0.4
KOH powder (10% m/v)[b]	24	33.1 ± 0.9
Mg/I_2 (0.5 g Mg/L)[b]		53.6 ± 0.6
3 Å molecular sieves (5% m/v)	24	77.3 ± 0.7
	48	46.8 ± 0.6
	72	34.2 ± 0.4
	120	26.5 ± 1.1
3 Å molecular sieves (10% m/v)	24	40.6 ± 0.6
	48	29.4 ± 0.8
	72	20.1 ± 0.6
	120	18.2 ± 0.9
3 Å molecular sieves (20% m/v)	24	28.1 ± 0.4
	48	23.1 ± 0.6
	72	19.2 ± 0.6
	120	10.5 ± 0.9

[a] Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b] Methanol was distilled from the desiccant once the magnesium had been consumed.

Toluene

Toluene can be predried using $CaCl_2$, CaH_2, or $CaSO_4$ and is most commonly dried by heating over sodium with benzophenone as indicator.[1] Such treatment (Na/benzophenone) reduced the water content from 225 ppm to about 34 ppm in our hands (Table 2). Storage of the "wet" toluene over 3 Å molecular sieves for 24 h or simple passage thereof over a column of silica readily provided "super dry" toluene with a moisture content in the low single digit ppm range. Either of these methods may be conveniently used to rapidly provide dry toluene suitable for the most demanding of reactions.

Dichloromethane

Dichloromethane is relatively easy to dry. It is not particularly hygroscopic, and even commercially available material has a low water content. Heating DCM over CaH_2 appears to be the method of choice for drying this solvent,[1] conditions which provided samples with a moisture content of about 13 ppm (Table 3). In contrast, simple storage of the solvent over activated 3 Å molecular sieves or passage thereof over a column of activated silica provided significantly drier material with very low water content in the single digit ppm range.

Acetonitrile

Acetonitrile is a polar, aprotic solvent with high solvating ability. It has a high affinity for water and can be difficult to dry.[1] Burfield[3b] found that P_2O_5 was particularly efficient at removing water from acetonitrile, where a desiccant loading of 5% (w/v) with 24 h of static drying leaves a residual water content of 9 ppm. In our hands, as was found for THF as described above, treatment of acetonitrile with 3 Å molecular sieves or neutral alumina readily gave solvent with very low residual moisture content (Table 4). Again, passage over neutral alumina followed by storage over 3 Å molecular sieves is a highly desirable method to rapidly and confidently secure access to dry acetonitrile. The reliability of the method was checked by making use of a larger sample size, namely 10.0 mL of the solvent for samples dried over 3 Å molecular sieves (10% m/v) for 24 h, providing essentially identical results to those derived from the smaller (3.0 mL) sample sizes.

Methanol and Ethanol

Lower alcohols are typically dried by heating over iodine-activated magnesium with a magnesium loading of 0.5−5.0 g/L.[1] Several other desiccants, including KOH, BaO, and CaO,[1,3] have also been recommended. KOH and Mg/I_2 are found to provide methanol with a water content of 33 and 54 ppm, respectively (Table 5). Molecular sieves (3 Å) were efficient at drying this solvent only when present at a loading of 10% m/v or higher and when the solvent was left to stand over the sieves for a minimum period of 72 h. Optimum drying is obtained with storage of the methanol over 20% m/v 3 Å molecular sieves for 5 days, by which time the water content reduces to about 10 ppm.

Ethanol behaved similarly, requiring a minimum of 10% m/v of activated 3 Å molecular sieves before efficient drying is noted, optimally also after a period of 5 days over 10% or 20% m/v of the sieves, under nitrogen (Table 6). Powdered KOH proved a rather active desiccant for methanol, and ethanol and may be used in a predrying step prior to storage

TABLE 6. Water Content in Ethanol after Drying[a]

desiccant	time (h)	residual water content (ppm)
none, “wet” solvent		1428.3 ± 3.8
KOH powder (10% m/v)[b]	24	26.4 ± 0.6
3 Å molecular sieves (5% m/v)	24	262.6 ± 2.0
	48	106.5 ± 0.7
	72	55.1 ± 0.9
	120	14.5 ± 0.4
3 Å molecular sieves (10% m/v)	24	186.1 ± 0.9
	48	69.5 ± 0.6
	72	36.9 ± 1.0
	120	12.3 ± 0.9
3 Å molecular sieves (20% m/v)	24	119.8 ± 0.7
	48	25.0 ± 0.7
	72	20.5 ± 0.5
	120	8.2 ± 0.4

[a] Drying was performed in triplicate; $n = 6$ for each dried solvent analyzed, providing $n = 18$ for each desiccant. [b] Ethanol was distilled from the desiccant.

over activated 3 Å molecular sieves to provide ultimate drying efficiency.

Conclusions

This work shows that the use of activated 3 Å molecular sieves, silica, or alumina readily and reliably provides dry solvents with residual moisture in the sub-10 ppm range. The method is practical, requires no special apparatus (apart from a column within which to house the silica or alumina and a two-necked flask for collecting the solvent under inert atmosphere using standard Schlenk techniques), and provides a safe method that does not make use of highly reactive materials such as sodium or metal hydrides. The developments here clearly indicate that laboratories currently making use of such methods could consider terminating such practices in favor of the safer methods detailed here which are, in the event, more efficient at drying solvents. [**CAUTION!** We did not test for the removal of peroxides from solvents such as tetrahydrofuran, so the usual precautions should be followed (such as testing for the presence of peroxides or performing a chemical quench of these reactive species[1]) with solvents for which the presence of peroxides may be an issue. For a discussion on the removal of peroxides, including the use of chemical and absorptive methods (with alumina and zeolites), the reader is advised to consult ref 7].

Experimental Section

Analytical reagent- or HPLC-grade solvents were obtained from commercial sources and used as is or were dried using the various methods described herein. Desiccants (3 Å molecular sieves, various silicas, neutral alumina) were obtained from commercial suppliers and were predried at 300 °C for 24 h immediately before use. Solvents were dried either by allowing them to stand over the desiccant under nitrogen or by passing the solvent over a column of the desiccant as specified, inside the glovebox. Each solvent was dried in triplicate. Each dried solvent was analyzed six times, providing $n = 18$ per solvent per desiccant. A coulometric Karl Fischer titrator fitted with a diaphragm cell (this setup is preferred for low-level moisture determinations) was used inside a glovebox under nitrogen (<1 ppm oxygen, <1 ppm moisture). Each part of the cell (anode and cathode) was charged with the appropriate commercial solution (Hydranal) suited thereto. The titrator was primed by allowing it to equilibrate and stabilize, which removes all residual water from the measuring cell. The accuracy of the titrator was measured against a 100 ppm certified reference material and gave an average reading of 98.3 ± 0.6 ppm water for 4.0 mL sample sizes (the amount of sample added was accurately determined by weighing the filled syringe and the empty syringe after injection of the sample, using a three decimal balance inside the glovebox) of the reference material, well within acceptable accuracy and precision ranges.

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Desiccant Efficiency in Solvent Drying. A Reappraisal by Application of a Novel Method for Solvent Water Assay

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The chemical literature, very inconsistent on the subject of the drying of solvents, abounds with contradictory statements as to the efficiency of even the more common desiccants. The recent advent of a novel, highly sensitive method which utilizes a tritiated water tracer for the assay of solvent water content has enabled the first comprehensive study to be made of the efficiency of various desiccants which pertains unambiguously to solvents. Benzene, 1,4-dioxane, and acetonitrile, chosen as model solvents, were wetted with known amounts of tritiated water and treated with a spectrum of desiccants, and the residual water contents were then assayed. The results range from the expected to the highly surprising. Some anomalous results, obtained for benzene and acetonitrile with acidic and basic desiccants, respectively, are discussed in terms of isotopic exchange reactions.

The bench chemist is often confronted by the problem of the selection of desiccants for solvent drying, and although dry solvents are frequently required for use in both preparative situations and in physicochemical studies, there is a paucity of *real* information in the literature. Some authors[2] are content to dismiss drying with statements such as "Frequently a liquid can be freed from water by shaking with a drying agent such as anhydrous calcium chloride or phosphorus pentoxide". In the field of organic synthesis, the situation is little better; different reference texts are replete with bewildering contradictions. Thus, magnesium sulfate, described as either neutral[3a,b,f] or acidic,[3c,e] is alternately an excellent drying agent, rapid in its action,[3a,b,d,f] or is slow,[3h] removing only small amounts of water.[4] Aluminum oxide is recommended mainly for use in desiccators,[3f] or as being preferred by many workers for ultimate solvent or reagent drying.[3g] Calcium chloride is "fast",[3b,d,4] or alternately "not rapid" [3f] in its action, and in any case, the consensus appears to be that calcium sulfate is to be preferred as a faster[3a,b,f] and a more efficient[3a,f] desiccant, even though the only existing quantitative comparison for solvents[4] shows the complete reverse to be true. Metallic sodium, generally agreed upon[3b,d] as being efficient, but slow in its drying action, is ridiculed as a desiccant by Plesch,[3g] who states that "the widespread use of sodium as a drying agent by organic chemists is more a ritual than an effective process". Furthermore, there is no doubt that many literature prescriptions for desiccation rely, at least to some extent, on the "chemical intuition" of the author, inspired perhaps by the existence of ubiquitous indices of siccative efficiency.[3a,b,d,f,5] These are usually based on the results of detailed studies of the comparative drying efficiency of desiccants which have been made with regard to the dryness of *gases*,[3h,6] and direct extrapolation to the condensed phase often gives misleading if not totally erroneous information. For example, phosphorus pentoxide, long considered the ultimate drying standard,[6] is actually quite mediocre in certain situations (vide infra). In summary, no comprehensive study of solvent drying comparable to that made for gases appears to exist, and since the efficiency of a desiccant is dependent on the nature of the solvent, this is a serious omission.

Recently,[7] an extremely sensitive method using a tritiated water tracer for the determination of solvent water content has been developed, where essentially drying efficiency is determined by addition of a specified amount of tritium-labeled water to a rigorously dried solvent and subsequent determination of the decrease in activity of the solvent after treatment with various drying agents. With the limitation that, owing to the problem of isotopic exchange, the method is not applicable to protic solvents, it provides a rapid and extremely precise assay of solvent water content. This has prompted us to undertake a comprehensive study of the efficiency of drying of a number of desiccants for the solvents benzene, 1,4-dioxane, and acetonitrile, representative of a spectrum of others commonly used in the laboratory. Thus, while benzene is a model for a useful range of aromatic and hydrocarbon solvents, and dioxane exemplifies commonly used ethers and bisethers, acetonitrile probably parallels the solvent behavior of a number of other polar, and, on account of its very high dielectric constant, perhaps dipolar aprotic solvents. Although selection of drying agents was generally made on the basis of common usage, some more esoteric examples which have been recommended for use in particular situations were also examined. The results have enabled us not only to present a sensible evaluation of many time-honored solvent drying recipes, but also to advocate the use of novel agents in previously unfamiliar situations.

Results and Discussion

Drying of Benzene. Static Drying. Benzene, despite its carcinogenic properties, is a widely used solvent, which, because of its ease of purification and relative inertness in many chemical systems, has been adopted as a secondary standard. Benzene has a zero dipole moment and on account of its low polarity has little affinity for water, the maximum solubility of water in this solvent being 0.063% w/w at 25 °C. Consequently, benzene is a relatively easy solvent to dry. Drying has been accomplished in the literature[8] with the following desiccants: phosphorus pentoxide, metallic calcium, sodium wire, calcium hydride, and molecular sieves.

In this study benzene containing 100 ppm of water was dried with a selection of the more useful and *efficient* desiccants. The results, summarized in Table I, apply to 5% w/v desiccant loadings and to static drying conditions at ambient temperatures (25–29 °C). Treatment with molecular sieves, alumina, silica gel, calcium hydride, and lithium aluminum hydride gave *super-dry*[9] solvents within 1 day. Alumina in particular was found to be an excellent desiccant for benzene, reducing the solvent water content below 0.01 ppm over this period. These findings thus corroborate earlier conclusions[10] that alumina is a particularly effective drying agent for hydrocarbons, previously exemplified by α-methylstyrene and β-pinene. The *apparent* increase in water content after drying for 7 days is most likely due to exchange or equilibria processes which occur between trace amounts of adventitious moisture—released from the surface of the glass vessel or perhaps gaining entry via diffusion through the *clearfit* stopper seal—and labeled water adsorbed on the desiccant. In any case, it is probably unrealistic to attempt to maintain water contents of below 0.01 ppm outside of totally sealed systems.

Table I. Efficiency of Various Desiccants for Static Drying of Benzene[c]

Registry no.	Desiccant	Residual solvent water content, ppm		
		6 h	1 day	7 days
	4 Å molecular sieves	2	0.03	0.06
1344-28-1	Al_2O_3	0.6	0.006	0.2
	Silica gel	0.3	0.3	0.1
7789-78-8	CaH_2	0.2		0.03
16853-85-3	$LiAlH_4$	3	2 (0.03)[a]	0.7
7440-23-5	Na	1.5	2 (2)[a]	4 (4)[b]
1314-56-3	P_2O_5	7	12	>28[b]
10043-52-4	$CaCl_2$	12	0.1	
7757-82-6	Na_2SO_4	>28	>28	>28

[a] Scintillation solution purged with nitrogen and recounted. [b] Distilled sample. [c] Desiccant loading 5% w/v; initial water content 100 ppm (0.01% w/w).

Table II. Effect of Stirring on the Drying Efficiencies of Desiccants for Benzene[b]

Desiccant	Residual solvent water content, ppm			
	6 h		1 day	
	Static	Stirred	Static	Stirred
$CaCl_2$	12	0.8	0.1	1
$LiAlH_4$	3	0.7	1.6	0.3 (0.02)[a]

[a] Purged with nitrogen and reassayed. [b] Desiccant loading 5% w/v; initial water content 100 ppm (0.01% w/w).

Calcium and lithium aluminum hydrides are both effective desiccants. The values for the complex metal hydride are apparently high through contamination of the solvent with labeled hydrogen resulting from interaction of the hydride with the labeled water. This was confirmed by recounting the sample after purging with nitrogen whereupon the *apparent* water content was reduced dramatically from 2 to 0.03 ppm. Interestingly, purging had little or no effect on samples dried with calcium hydride and sodium, and this parallels a qualitative observation that lithium aluminum hydride, perhaps because of its finely divided form, appears to *bind* the hydrogen, viz., gas bubbles can still be released from the desiccant long after the solvent is essentially dry.

Sodium is observed to reduce the water content extensively within the first 6 h, but subsequently the *apparent* water content is seen to increase significantly. Since purging with nitrogen and distillation do not reduce the figure it may be speculated that sodium is actually able to metalate benzene, necessarily at an extremely low rate. Tritiation could then occur by reaction of organosodium intermediates with trace amounts of newly formed tritiated water, whose genesis would be identical with that proposed above.

Phosphorus pentoxide appears to be an ineffective drying agent. However, this conclusion must be tempered by the significant increase in *apparent* water content with time of drying. An increase of such magnitude can only reasonably be explained by the presence of exchange reactions. Indeed, phosphoric acid catalyzed exchange reactions have been used elsewhere[11] for the synthesis of tritiated aromatic compounds. The presence of exchange reactions thus unfortunately precludes any conclusion as to the efficiency of phosphorus pentoxide as a desiccant for benzene.

Calcium chloride is seen to be an effective drying agent, quite capable of giving *super-dry* benzene. In contrast, sodium sulfate is completely inept, and the samples obtained after drying were too active for direct counting, indicating little or no drying.

Effect of Stirring. The effect of stirring on rapidity of drying was investigated for calcium chloride and lithium aluminum hydride (Table II). In both cases stirring has an accelerating effect on drying. This is most likely due to breakdown of particle size which increases the effective desiccant surface rather than diffusion control of the drying process, since finely divided silica gel is a very rapid desiccant even under static drying conditions (Table I).

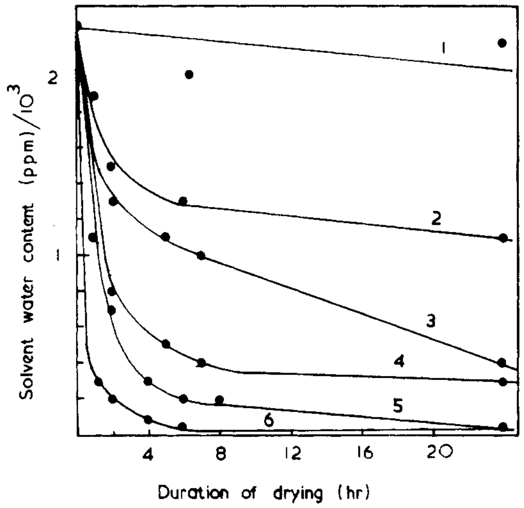

Figure 1. Drying of dioxane with various desiccants. Experimental conditions as for Table III. 1, $MgSO_4$; 2, KOH pellets; 3, P_2O_5; 4, $CaCl_2$; 5, 4 Å molecular sieves; 6, CaH_2.

Drying by Distillation. Fractionation of benzene with retention of the middle fraction, a time-honored process, has frequently been advocated as a method of drying. In this work it was found that the middle fraction, after discarding the first 20%, contained 15 ppm of water. This is significantly drier than the initial water content, but the drying pales in comparison with static drying by the majority of desiccants (Table I).

Drying of Dioxane. Static Drying. Dioxane, although not a very polar solvent (μ = 0.45), is completely miscible with water and is consequently far more difficult to dry than benzene. Drying is frequently tackled in at least two stages. Preliminary drying agents[8] include potassium hydroxide, calcium chloride, sodium hydroxide, and magnesium sulfate, whereas final drying[8] has been accomplished almost exclusively with sodium and occasionally with sodium–lead alloy.

In this study dioxane with an initial water content of 2300 ppm (0.23% w/w)[12] was dried with a selection of both preliminary and final drying agents. The initial rate of drying for a selection of desiccants is displayed in Figure 1. It is immediately apparent that magnesium sulfate is almost completely ineffective as a drying agent, whereas calcium hydride is both rapid and efficient. It is also interesting that, for the first 24 h at least, the speed of drying parallels desiccant efficiency. Remarkably, phosphorus pentoxide does not excel as a drying

Table III. Efficiency of Various Desiccants for Static Drying of Dioxane[c]

Registry no.	Desiccant	Residual solvent water content, ppm 6 h	1 day	7 days
	Na		20	6
	Na–K alloy	132 (22)[a]	22 (11)[a]	22 (6)[b]
	CaH_2	50	30	23
	4 Å molecular sieve	200	40	26
1310-58-3	KOH (ground)	204	150	14 (8)[b]
	$CaCl_2$	450	300	300
	P_2O_5	1050	400	60
	$LiAlH_4$	1200	900	1100 (340)[b]
	KOH (pellets)	1300	1100	200
	Silica gel	1300	1300	1200
	Al_2O_3		1700	1400
7778-18-9	$CaSO_4$		1600	1500
	Na_2SO_4		1900	1800
7487-88-9	$MgSO_4$		2200	2200

[a] After purging to remove H_2. [b] After distillation from desiccant. [c] Desiccant loading 5% w/v; initial water content 2300 ppm (0.23% w/w).

agent, being surpassed in both speed and efficiency by even calcium chloride.

Results for a wider range of desiccants and drying times are summarized in Table III. Sodium, sodium–potassium alloy (containing 80% by weight of potassium), calcium hydride, and molecular sieves are all seen to be very effective drying agents, although at these initial water loadings none of them dry dioxane to *super-dry* levels, which, however, could undoubtedly be achieved by repetitive drying. Sodium–potassium alloy, typically described as possessing a higher drying intensity than metallic sodium,[3h] has been advocated as a siccative in situations where extreme desiccation is required,[13] where its principal advantage over sodium, i.e., its liquid state at ambient temperatures, should expedite very efficient drying of solvents boiling below the melting point of the alkali metal. It is somewhat remarkable therefore that the alloy is not superior to sodium granules under static drying conditions. Powdering of KOH pellets is seen to have a dramatic effect on the rapidity *and* efficiency of drying, and supports a previous report[3c] that drying of diethyl ether and THF solely by treatment with powdered KOH gives material which is immediately suitable for the preparation of reactive organometallics. It is striking that powdered KOH, although slightly slower in action, actually surpasses calcium hydride and molecular sieves in ultimate efficiency.

$LiAlH_4$, though described as highly effective for drying ethers,[3h] actually appears strangely ineffective. The very high residual water contents cannot be explained in terms of labeled hydrogen contamination, and it is difficult to invoke any other interferences. A probable conclusion is that unlike CaH_2, $LiAlH_4$ is not effective under conditions of high initial water content, and this result must cast some doubt on its unqualified recommendation as a desiccant for THF.[14]

The almost complete ineffectiveness of alumina and silica gel for dioxane drying is a complete reversal of their behavior with benzene. This underscores the risks involved in extrapolating the results of gas drying to the liquid phase.

Magnesium and sodium sulfates are again[4] found to be slow and ineffective at these water concentrations. Sodium sulfate, in particular, has earlier[4] been shown to be an almost completely inept desiccant for ethers at *much higher* water concentration, viz., the water content of diethyl ether was reduced from 2.07% w/w to merely 1.83% w/w after a period of several weeks. The value of sodium sulfate, even as a preliminary drying agent, must therefore be questionable. In view of its unanimous recommendation, calcium sulfate also rates surprisingly poorly.

Table IV. Effect of Conditions on the Drying of Dioxane[a]

Desiccant	Drying time, h	Residual solvent water content, ppm Static	Refluxed	Stirred
CaH_2	2	200	110	
	6	50	29	
	24	30	14	4
	168	23		2
Na	24	20	5	
	48		3	

[a] Desiccant loading 5% w/v; initial water content 2300 ppm (0.23% w/w).

Table V. The Use of Visual Indicators in Dioxane Drying

Desiccant–indicator	Residual solvent water content after distillation, ppm
Sodium–benzophenone	20
BuLi[b]–triphenylmethane	22
BuLi–phenanthroline	17
Trityl fluoroborate[c]	650 (800)[a]

[a] As determined by the near IR method. Initial water content 2300 ppm (0.23% w/w). [b] Registry no., 109-72-8. [c] Registry no., 341-02-6.

Effect of Stirring and Refluxing on Drying. Since solvents are frequently dried by refluxing over desiccants such as sodium and calcium hydride, the effect of refluxing was briefly investigated. It can be seen (Table IV) that while refluxing dioxane over CaH_2 results in moderate increases in efficiency and speed of drying, stirring is seen to be much more effective.

Refluxing over sodium (Table IV) is seen to give an improvement in efficiency compared to static drying but prolonged refluxing is not particularly beneficial.[15] It is worthy of note that stirring over calcium hydride at ambient temperatures is as effective as refluxing over molten sodium.

Drying Agents with Visual Indication. Although desiccation prescriptions which include a visual indication of solvent dryness have become fairly common in recent years, no quantitative measure of their efficiency appears to have been made. These methods generally involve the in situ generation of small amounts of colored, highly moisture-sensitive intermediates, often by the action of the desiccant on an added "indicator", and the solvent presumed anhydrous when the indicator color persists. Table V, which displays a selection

Table VI. Efficiency of Various Desiccants for Static Drying of Acetonitrile

Registry no.	Desiccant	Residual solvent water content, ppm	
		1 day	7 days
	P_2O_5	9 (12)[a,b]	5
	3 Å molecular sieves	49	27
1303-86-2	B_2O_3	59[a]	
584-08-7	K_2CO_3	250	1300
	4 Å molecular sieves	450	500
	$CaCl_2$	1200	2200
	Silica gel	1300	1300
	Al_2O_3	1600	1700
	CaH_2	1900	1900[a] (1300)[a,c]
	KOH (powdered)	2200[a,b,d]	
	KOH (pellets)	2500	1300
	$CaSO_4$	2500	2200
	$Ph_3C^{+-}BF_4$	2700[a] (2800)[a,c]	

[a] Distilled sample. [b] Colored residue. [c] By near IR method. [d] Strong amine smell in distillate. [e] Desiccant loading 5% w/v; initial water content 2800 ppm (0.28% w/w).

of those investigated for dioxane, reveals that although none of them give *super-dry* solvent (see, however, discussion below), the first three entries give comparable results to the best of those obtained for dioxane after static drying for 1 day (Table III). The intense blue sodium ketyl of benzophenone (entry 1), often used in the preparation of absolute diethyl ether,[16] where it presumably also serves to remove peroxides, gives similar results to butyllithium. The appearance of the red triphenylmethyl anion (entry 2) has been advocated as an indicator in the preparation of "anhydrous" THF.[17] We have found that if no special precautions, e.g., anaerobic conditions, are utilized, then the amount of butyllithium required to impart a persistent color to the solvent is excessively high, owing perhaps to consumption of the "indicator" by molecules other than water, e.g., oxygen. This shortcoming led to an experiment with 1,10-phenanthroline (entry 3), previously suggested as an indicator in the "alcohol method" of assaying BuLi.[18] The formation of the derived rust-red complex required only about half the butyllithium used in entry 2, and since the result was a slightly drier solvent, the use of this indicator is to be preferred. In the general context of the butyllithium experiments, it must also be pointed out that it is known that alkyllithiums react relatively slowly with THF,[19] to give, initially, 2-lithiotetrahydrofuran, which, if the analogous reaction were to occur with dioxane, may serve to label the ether, and hence raise the *apparent* water content, by reaction of metalated dioxane with tritiated water. While this reaction has not been reported for dioxane, and in any case would be expected to be extremely slow compared to reaction of the alkyllithium with water, some inflation of the *apparent* water content by this means cannot be altogether ruled out. Although trityl fluoroborate (entry 4) has not been previously used as a desiccant for ethers, it has been used to dry acetonitrile (vide infra), and this experiment was run to determine its efficiency in a different solvent type. Even though, at this solvent water concentration, the deep yellow color of the salt solution was not discharged, the recovered ether contained a surprisingly large amount of residual water, and this result was cross-checked by the near IR method. Compared to entries 1 to 3, trityl fluoroborate gives poor ultimate drying, which however, is still better than that obtainable with lithium aluminum hydride (Table III).

Drying of Acetonitrile. Static Drying. Acetonitrile, a polar aprotic solvent ($\mu = 3.44$) of high solvating power and favorable physical properties, has been widely used as a solvent both in the study of chemical reactions and for physical measurements involving spectrophotometric and electrochemical techniques. However, because of its high affinity for water it is an outstandingly difficult solvent to completely dry. Drying is conventionally accomplished[8] by treatment with preliminary drying agents such as anhydrous sodium or potassium carbonate, anhydrous calcium chloride, silica gel, or 3 Å molecular sieves, and final drying with calcium hydride, phosphorus pentoxide, or more recently with trityl fluoroborate.[20]

The results of static drying with a range of desiccants are displayed in Table VI. In contradistinction to the other solvents investigated phosphorus pentoxide is seen to excel in its drying efficiency, but even so *super-dry* acetonitrile is not obtained. It is interesting to note that the residual water content is of similar order of magnitude to an earlier result which also utilized P_2O_5.[21] The only disadvantage to phosphorus pentoxide drying is the partial loss of solvent through polymerization, and possible contamination by desiccant residues.[22] Reasonably effective drying can also be achieved with 3 Å molecular sieves which reduce the water content to less than 30 ppm after 1 week. The relative inefficiency of 4 Å sieves emphasizes the need for careful selection of sieve pore size for effective drying. A hitherto little mentioned[3f] but useful desiccant is boric anhydride. Direct sampling proved impossible in this case since soluble desiccant residues interfered visually with the scintillant, but the sample distilled after 1 day stirring with the anhydride had a water content of 59 ppm. This reagent is advantageous compared to phosphorus pentoxide since it does not induce polymerization of the solvent nor does it appear to be significantly volatile. It also offers advantages in its ease of handling and disposal.

Silica gel and alumina are again, as with dioxane, largely ineffective. This may reflect their rather low capacity for effective drying at high water contents,[3g] but in any case makes them an unlikely choice for preliminary drying. Calcium sulfate, although generally strongly recommended for efficient drying, is seen to be the least effective of the examined desiccants, and is clearly surpassed by the underrated calcium chloride.[23]

The ineffectiveness of the previously excellent desiccants potassium hydroxide and calcium hydride seems anomalous. Careful examination of the results reveals that all the basic siccatives, potassium hydroxide, calcium hydride, and potassium carbonate, give apparently little drying. In addition the *apparent* water content in the presence of the weakly basic potassium carbonate increases very significantly from 251 to 1300 ppm over the course of 1 week. These observations appear indicative of a base-catalysed exchange reaction, viz.

$$CH_3CN + T_2O \overset{^-OH}{\rightleftharpoons} CH_2TCN + HOT$$

Such base-catalyzed exchange reactions of the α hydrogens have been previously encountered with β-hydroxypropionitrile[24] but rather surprisingly it has been claimed[25] that acetonitrile itself does not exhibit similar behavior. In an attempt to confirm the presence of exchange reactions, the tracer experiment was cross-checked by the near IR method for the calcium hydride case. The near IR value of the water content is significantly lower, and this is suggestive of the presence of exchange reactions. Most unexpectedly, this determination also revealed that calcium hydride is largely ineffective for drying acetonitrile. This remarkable observation, together with the results for phosphorus pentoxide drying, undermines the intuitive assumption that the relative efficiencies of desiccants should, barring chemical incompatibility, be independent of solvent type.

The interference, by exchange reactions, unfortunately makes it impossible to draw many conclusions on the efficiency of the basic desiccants save that potassium carbonate is clearly a reasonable desiccant, at least for preliminary drying.

It is worthy of mention that drying with finely powdered potassium hydroxide gave rise to a colored residue and a significant amine content in the distilled fraction.[26]

Trityl Fluoroborate. The use of this stable, orange carbenium ion salt as a desiccant for acetonitrile would seem to be advantageous; it can be stored in a desiccator for extended periods without decomposition,[27] and is used as a siccative[20] simply by adding it in small batches to the wet nitrile until a strong yellow color persists, thus furnishing a visual indication of dryness. The results obtained by using this and the IR method are displayed in Table VI, and indicate that, at these water concentrations, the carbocation salt is a spectacularly ineffective desiccant. The reason for this impotence seems obscure, although acetonitrile, by virtue of its solvation ability, has a well-known moderating influence on the stability of carbenium ions,[28] and indeed, the drying of dioxane by trityl fluoroborate (vide supra) is significantly better than the present solvent. Whatever the true reason, it is clear that, as a desiccant for acetonitrile, the salt is completely worthless.

Merits of the Study. The present study should be of considerable heuristic value, particularly to the bench chemist in the provision of *directly* relevant data, and it is also worthwhile briefly emphasising again[7] that for reasons which include (1) contamination of the solvent by desiccant residues and possibly labeled hydrogen, (2) exchange reactions, and (3) the kinetic isotope effect, the *apparent* water contents, as reported above, will always represent the upper limits of the true content. Of course, this in no way detracts from the value of the work, and, to cite an example, merely means that it is entirely possible that alumina is able to dry benzene to below 6×10^{-3} ppm!

Experimental Section

Radioactive samples were assayed in a scintillation solution containing 0.4 g of 1,4-bis(5-phenyloxazol-2-yl)benzene (POPOP) and 4.0 g of 2,5-diphenyloxazole (PPO) per liter of toluene with a Beckman Model LS-100 liquid scintillation spectrometer. Determination of water content by the near IR method was performed using a Unicam SP700 spectrophotometer.[29] Tritium-labeled water was purchased from the Radiochemical Centre, Amersham, England, at an initial activity of 5 Ci/mL and was diluted with appropriate quantities of inactive water.

Desiccants. Lithium aluminum hydride and phosphorus pentoxide were used as supplied; calcium hydride (99.5%) and reagent grade potassium hydroxide were rapidly powdered immediately prior to use in a mortar and a mechanical blender, respectively. Chromatographic grades of neutral alumina (activity 1) and silica gel, as well as calcium, magnesium, and sodium sulfates, calcium chloride, potassium carbonate, and 3 and 4 Å molecular sieves were activated for 15 h at 300–320 °C before use. Since hydration occurs rapidly on cooling of these desiccants in moist air, cooling was carried out in a phosphorus pentoxide desiccator, and the samples then used immediately. Sodium metal, whose oxide crust had previously been removed by melting under xylene, was cut into 2-mm cubes under dry petroleum ether. Sodium–potassium alloy was prepared as detailed elsewhere[30a] from oxide-free metals. (It is worth noting that the fire hazard associated with destroying excess alloy is completely avoided if the disposal is carried out in two steps. Addition of a little dry ethyl acetate to the alloy in dioxane smoothly consumes potassium—presumably via an acyloin reaction. Unreacted sodium can then be destroyed conventionally using ethanol.) Trityl fluoroborate[27] and boric anhydride[3f] were respectively prepared from triphenylcarbinol and tetrafluoroboric acid, and by high-temperature (900 °C) dehydration of boric acid.

Solvents. Benzene. AR grade reagent was stirred for 24 h with finely ground calcium hydride, refluxed, carefully fractionated (bp 80.0 °C), and stored over 4 Å molecular sieves.

1,4-Dioxane. Commercial 1,4-dioxane was purified and dried according to a method cited by Fieser,[30b] whereby the glycol acetal impurity is removed by hydrolysis to acetaldehyde, which is itself voided by purging with nitrogen gas. Preliminary drying with potassium hydroxide pellets followed by fractionation (bp 101–101.5 °C) from sodium gave material which was stored in a dark bottle over 4 Å molecular sieves.

Acetonitrile. Following well-documented procedures,[8] reagent grade material, after being given a preliminary drying with potassium carbonate (24 h), was decanted on to phosphorus pentoxide and stirred at reflux for 2 h. Fractionation gave material of bp 81.5 °C, which was not stored, but used immediately.

Techniques. The procedure used for benzene serves as an example. A stock solution of benzene containing 100 ppm of labeled water was prepared by the addition of 18 μL of tritiated water, specific activity 40 mCi/mL, to 180 g of purified benzene; homogenization was accomplished by stirring overnight. Aliquots of the stock solution (15.0 ± 0.1 mL) were syringed directly onto 0.75 ± 0.03 g of activated desiccant contained in a 25-mL clear-fit round-bottom flask, which was then stoppered. Where appropriate samples were stirred magnetically. Samples (1.00 ± 0.02 mL) were taken at time intervals specified in the text—care was taken to avoid disturbing the desiccant—and syringed directly into the counting vials. Where possible, samples were distilled from the desiccant so as to provide a cross-check against contamination of the solvent by labeled desiccant residues. Samples were accumulated and assayed batchwise.

Similar procedures were used with dioxane and acetonitrile, except that higher water contents were examined and tritiated water of low specific activity (0.5 mCi/mL) was employed.

Registry No.—Benzene, 71-43-2; dioxane, 123-91-1; acetonitrile, 75-05-8.

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Perhydrogenation of 2,8-Diaminopurine

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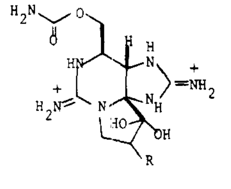
2,8-Diaminopurine (**7**) can be hydrogenated over PtO_2 in acidic medium to give 2-imino-4-guanidinomethyl-5-imidazolidinone (**11**) which can itself be further hydrogenated to 2-imino-4-guanidinomethylimidazolidine (**12**). The structures of **11** and **12** were proven by unambiguous synthesis. 2,8-Diamino-6-methylpurine (**37**) also can be hydrogenated in a similar manner to two analogous compounds, as isomeric mixtures, whose structures are inferred by comparison with **11** and **12**. A superior method has been developed for synthesizing the diaminopurines **7** and **37**, involving the condensation of the appropriate triaminopyrimidine with *N*-(methylmercaptochloromethyl)-*p*-toluenesulfonimide (**20**) followed by ring closure via the carbodiimide and detosylation with HF.

Saxitoxin is one of the most potent naturally occurring neurotoxins. It is the sole toxin produced by the marine dinoflagellate *Gonyaulax catenella*[1] and is a minor constituent of the toxins produced by *G. tamarensis.*[2] Ingestion of these dinoflagellates by several species of normally edible shellfish is frequently responsible for their toxicity to man. X-ray crystallographic analysis of two derivatives, the bis-*p*-bromobenzenesulfonate[3] and the ethyl hemiketal dihydrochloride,[4] have established structure **1** for crystalline saxitoxin hydrate, and ^{13}C NMR studies have also established this structure for the molecule in solution.[4] Recently[5] the major toxins of *G. tamarensis*, gonyautoxins II and III, also existing as the hydrates, were postulated to have the closely related structures **2** and **3**, respectively.



1, R=H
2, R=α-OH
3, R=β-OH

Saxitoxin and the gonyautoxins are unique among natural products in that their structures incorporate a tetrahydropurine moiety composed of two guanidine units fused together in an azaketal linkage which remains intact under ordinary conditions. We were therefore interested in preparing a simple model of the tetrahydropurine backbone of saxitoxin, devoid of the fused ketone bearing ring and the peripheral carbamate, for both chemical and biological investigations. We chose to study the catalytic hydrogenation of 2,8-diaminopurine (**7**), which conceivably could lead to 2,8-diiminotetrahydropurine (**10**) or its tautomers, the simplest possible tetrahydropurine model of saxitoxin. We now report the results of our study of the heterogeneous catalytic hydrogenation of 2,8-diaminopurines.

The literature relating to the catalytic reduction of purines is relatively meager. 1,6-Dihydropurine (**5**) has been prepared[6,7] from purine and 6-chloropurine (**4**), and in weak acid **5** was hydrolyzed to 4(5)-aminomethyl-5(4)-aminoimidazole (**6**). Similarly a tetrahydropurine is claimed[8] to result from catalytic reduction of 2,6,8-trichloropurine. More recently,[9] the catalytic reduction of 2,8-diaminopurine (**7**) is reported to yield a compound whose structure was assigned as 2-amino-5-guanidino-1,4,5,6-tetrahydro-6-oxopyrimidine (**8**). These authors also report the preparation of 2,8-diamino-4,5,6,9-tetrahydro-1,7,9-trimethylpurine by sodium borohydride reduction of 2,8-diamino-1,7,9-trimethylpurine, and claim to have electrolytically reduced **7** to **8** plus tetrahydropurine **10**, obtained as an inseparable mixture with another reduction product **9**.

In contrast to that report, we have found that **7** is slowly hydrogenated with a PtO_2 catalyst in hydrochloric acid (pH 1.5) at room temperature and 20 psi pressure to give a single product, A, in quantitative yield. A could be further reduced under more drastic conditions (60 °C, 100 h) to give another product, B, also in quantitative yield. The ^{1}H NMR spectrum of A·2HCl consisted of a doublet (2 H, J = 5 Hz) and a triplet (1 H, J = 5 Hz); its ^{13}C NMR spectrum is tabulated in Table I.

These NMR data suggested that A was not a reduced purine with an intact bicyclic ring system but rather the five-membered monocyclic imidazolidinone **11**. The ^{13}C NMR absorption at δ 173 is clearly assigned to the amide carbonyl, and the simple doublet–triplet pattern of the ^{1}H NMR spectrum implies the freely rotating methylene group of **11**. The alternative six-membered ring structure **8** previously proposed[9] for the 2,8-diaminopurine reduction product should display