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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 authors² 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 solvents⁴ 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 literature⁸ 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 conclusions¹⁰ 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
1344-28-1	4 Å molecular sieves	2	0.03	0.06
	Al ₂ O 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 ₂ O ₅	7	12	>28 ^b
10043-52-4	CaCl ₂	12	0.1	
7757-82-6	Na ₂ SO 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 elsewhere¹¹ 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

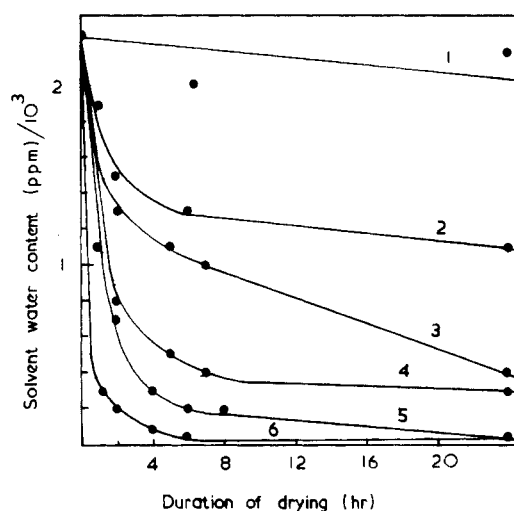


Figure 1. Drying of dioxane with various desiccants. Experimental conditions as for Table III. 1, MgSO₄; 2, KOH pellets; 3, P₂O₅; 4, CaCl₂; 5, 4 Å molecular sieves; 6, CaH₂.

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).

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 ($\mu = 0.45$), 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 agents⁸ include potassium hydroxide, calcium chloride, sodium hydroxide, and magnesium sulfate, whereas final drying⁸ 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 ₂ O ₅	1050	400	60
	LiAlH ₄	1200	900	1100 (340) ^b
	KOH (pellets)	1300	1100	200
	Silica gel	1300	1300	1200
	Al ₂ O ₃		1700	1400
7778-18-9	CaSO ₄		1600	1500
	Na ₂ SO ₄		1900	1800
7487-88-9	MgSO ₄		2200	2200

^a After purging to remove H₂. ^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.

LiAlH₄, 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 CaH₂, LiAlH₄ 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 again⁴ found to be slow and ineffective at these water concentrations. Sodium sulfate, in particular, has earlier⁴ 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.

Effect of Stirring and Refluxing on Drying. Since sol-

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.

vents 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 CaH₂ 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 ₂ O ₅	9 (12) ^{a,b}	5
	3 Å molecular sieves	49	27
1303-86-2	B ₂ O ₃	59 ^a	
584-08-7	K ₂ CO ₃	250	1300
	4 Å molecular sieves	450	500
	CaCl ₂	1200	2200
	Silica gel	1300	1300
	Al ₂ O 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 ₃ C ⁺ -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 alkylolithiums 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 alkylolithium 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).

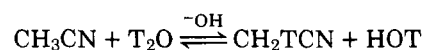
Drying of Acetonitrile. Static Drying. Acetonitrile, a polar aprotic solvent ($\mu = 3.44$) of high solvating power and favorable physical properties, has been widely used as a solvent both in the study of chemical reactions and for physical measurements involving spectrophotometric and electrochemical techniques. However, because of its high affinity for water it is an outstandingly difficult solvent to completely dry.

Drying is conventionally accomplished⁸ 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 P₂O₅.²¹ 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.



Such base-catalyzed exchange reactions of the α hydrogens

have been previously encountered with β -hydroxypropionitrile²⁴ but rather surprisingly it has been claimed²⁵ 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 siccative²⁰ 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 emphasizing again⁷ 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 fluoroborate²⁷ 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 μ L 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 \pm 0.1 mL) were syringed directly onto 0.75 \pm 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 \pm 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.

References and Notes

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Perhydrogenation of 2,8-Diaminopurine

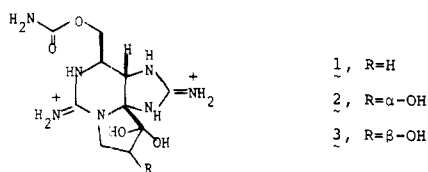
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2,8-Diaminopurine (7) can be hydrogenated over PtO₂ in acidic medium to give 2-imino-4-guanidinomethyl-5-imidazolidinone (11) which can itself be further hydrogenated to 2-imino-4-guanidinomethylimidazolidine (12). The structures of 11 and 12 were 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*-bromobenzenesulfonate³ and the ethyl hemiketal dihydrochloride,⁴ have established structure 1 for crystalline saxitoxin hydrate, and ¹³C NMR studies have also established this structure for the molecule in solution.⁴ Recently⁵ 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.



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 azaketall 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 claimed⁸ 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 PtO₂ 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 ¹H NMR spectrum of A·2HCl consisted of a doublet (2 H, *J* = 5 Hz) and a triplet (1 H, *J* = 5 Hz); its ¹³C 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 ¹³C NMR absorption at δ 173 is clearly assigned to the amide carbonyl, and the simple doublet-triplet pattern of the ¹H NMR spectrum implies the freely rotating methylene group of 11. The alternative six-membered ring structure 8 previously proposed⁹ for the 2,8-diaminopurine reduction product should display