

Chapter Four

GLYCOALKALOIDS OF THE SOLANACEAE

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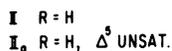
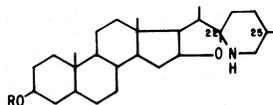
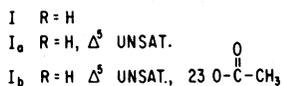
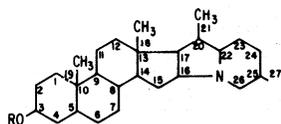
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Introduction

The Chemistry of the Glycoalkaloids
The Biosynthesis of Glycoalkaloids
Glycoalkaloid Distribution in the Plant
Biological Activity
Toxicity of Glycoalkaloids
Conclusion

INTRODUCTION

Glycoalkaloids are nitrogenous steroidal glycosides that are found in most *Solanum* species. Defosses, in 1820,¹ reported that the active principle of morel (*S. nigrum*) was an organic base which he named solanine. Baup² reported the presence of solanine in potatoes and concluded it "will find a use in medicine..." More than a century later, *Solanum* glycoalkaloids have become important starting compounds for the commercial preparation of steroidal hormone intermediates. Glycoalkaloid research has not been restricted to chemical studies; the biological activity of these compounds has been extensively investigated, primarily in the context of plant resistance to pests and microorganisms and of human toxicity. The presence of glycoalkaloids in foods such as potatoes, tomatoes, and eggplant has always been of great concern; understandably, this concern has generated much research activity.



<u>Glycoalkaloid</u>	<u>Aglycone</u>	<u>Aglycone Structure</u>	<u>R Carbohydrate</u>
α-Solanine	Solanidine	I _a (20S,22R,25S)	Solatriose
α-Chaconine	Solanidine	I _a (20S,22R,25S)	Chacotriose
Solasonine	Solasodine	II _a (22R,25R)	Solatriose
Solamargine	Solasodine	II _a (22R,25R)	Chacotriose
Tomatine	Tomatidine	II (22S,25S)	Lycotetraose
Solacauline	Soladulcidine	II (22R,25R)	Polyatriose
α-Solamarine	Tomatidenol	II _a (22S,25S)	Solatriose
β-Solamarine	Tomatidenol	II _a (22S,25S)	Chacotriose
Demissine	Demissidine	I (20S,22R,25S)	Lycotetraose
Leptine I	Acetylleptinidine	I _b (20S,22R,25S)	Chacotriose
Leptine II	Acetylleptinidine	I _b (20S,22R,25S)	Solatriose
Commersonine	Demissidine	I (20S,22R,25S)	Commertetraose

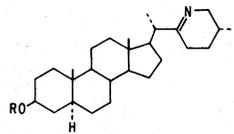
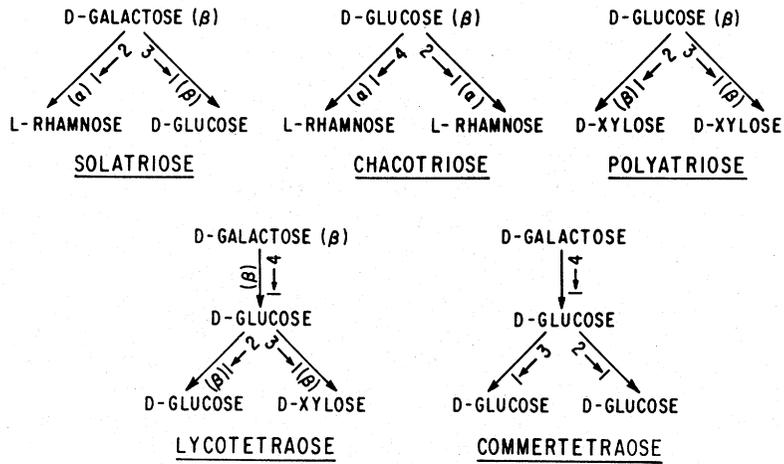
Excellent reviews of the chemistry of glycoalkaloids include those by Prelog and Jeger^{3,4} and Schreiber.⁵ There is also a comprehensive review of tomatine chemistry and biology⁶ and one of the glycoalkaloid literature emphasizing health-related research.⁷ In this chapter many aspects of the chemistry, biochemistry and biology of the glycoalkaloids are discussed, with emphasis on research reported within the last ten years.

THE CHEMISTRY OF THE GLYCOALKALOIDS

The glycoalkaloid composition of more than 250 Solanum species has been determined.⁵ The structures of many of these compounds are listed in Tables 1 and 2. The aglycone skeletal structure is either of the solanidane (I) or spiro-solane (II) type. Minor structural variations of these two ring systems such as Δ^5 unsaturation or isometrization at C-22 account for most of the other aglycones listed in Table 1. The carbohydrate moieties listed in Table 2 can be found in combination with a number of different aglycones; for example, chacotriose is found in α -chaconine (solanidine aglycone), β -solamarine (tomatidenol aglycone) and solamargine (solasodine aglycone). Thus the multiplicity of glycoalkaloids found in Solanum species stems from minor modification of the aglycone structure and various combinations of aglycone and carbohydrate moieties. The compilation in Tables 1 and 2 is not meant to be complete; minor glycoalkaloids and compounds that may be derived from higher saccharides by hydrolysis (the removal of a rhamnose from α -chaconine yields β -chaconine) have been omitted. In the latter case, these compounds are artifacts produced by the action of hydrolytic enzymes released when the tissue is excised from the plant. If the enzymatic activity of S. tuberosum detached flowers is not immediately quenched, copious amounts of β -chaconine are produced; however, when precautions are taken to destroy post harvest enzymatic activity, β -chaconine is isolated only in minor amounts and α -chaconine is the predominant glycoalkaloid. Therefore, unless the proper precautions are taken, the origin of glycoalkaloids that may be derived from other glycoalkaloids by loss of sugar(s) is uncertain.⁵

It was not until the 1940's that characterization of Solanum glycoalkaloids was undertaken. The outstanding research of Prelog, Kuhn and Schreiber has contributed

TABLE 2
STRUCTURE OF GLYCOALKALOID CARBOHYDRATE MOIETIES



- III R = H (CONGESTIDINE)
- III_a R = GLUCOSE, GALACTOSE
- III_b R = GLUCOSE, XYLOSE, RHAMNOSE
- III_c R = GLUCOSE, XYLOSE

Figure 1. Glycoalkaloids

significantly to our knowledge of glycoalkaloid structures. Relatively few new glycoalkaloids have been discovered in the last ten years. The commercial importance of solasodine (or tomatidenol) as a precursor to the steroidal hormone intermediate 3β -acetoxy-pregna-5,16-diene-20-one has been the primary incentive for continued characterization of the glycoalkaloid composition of the Solanum species. Solasodine glycoalkaloids recently isolated and characterized are listed in Table 3. Solatifoline was shown to be different than solasonine (Table 1) by x-ray analysis, although it contains the same aglycone and sugars.

New glycoalkaloids, containing the novel aglycone congestidine (III), isolated from S. congestiflorum and characterized by Katz et al.¹³ are: solacongestinine (III_a), α -solacongestinine (III_b), and β -solacongestinine (III_c) as shown in Figure 1.

Modern methods of structural analysis have greatly facilitated glycoalkaloid characterization. Radeaglia et al.¹⁴ and Weston et al.¹⁵ have reported the ¹³C-NMR spectra of tomatidine, solasodine, soladulcidine, solanidine, and demissidine. With few exceptions, the shift assignments are unambiguous. The structure of the carbohydrate moiety can now be determined by a modified permethylation method. The methylated sugars resulting from hydrolysis of the permethylated glycoalkaloid are characterized by combined gas chromatography - mass spectrometry of the alditol acetate derivatives¹⁶ rather than the older classical methods¹⁷ which required substantially larger quantities for identification.

Recently effort has been devoted to developing methods for total glycoalkaloid (TGA) analysis because of the suspected toxic activity of these compounds. Zitnak⁷ reviewed many of the available TGA methods. Most of these methods are a compromise, since it is difficult to isolate, in quantitative yield, a glycoalkaloid fraction that is suitable for accurate analysis by either colorimetric or gravimetric methods. Some of these methods also require the presence of functional groups that are not common to all glycoalkaloids such as olefinic unsaturation for the formaldehyde-sulfuric acid reaction.¹⁸ A method based on titration of the free aglycone has been described;^{19,20} this method does not require extensive preliminary purification of the glycoalkaloid fraction and will measure all

TABLE 3
NEW SOLASODINE GLYCOALKALOIDS

Glycoalkaloid	Carbohydrate ^a	<u>Solanum</u> species	Reference
Solardixine	-gal ³⁻¹ —glu ²⁻¹ —glu ²⁻¹ —rham	<u>S. lactiniatum</u> <u>S. khasianum</u>	Bite <u>et al.</u> ⁸
Solasurine	-glu—rham	<u>S. elaeagnifolium</u> <u>S. aviculare</u>	Seth and Chatterjee ⁹
Solashabanine	gal,3 glu, rham	<u>S. lactiniatum</u>	Bite and Shabana ¹⁰
Solaradinine	gal,4 glu, rham	<u>S. lactiniatum</u>	Bite and Shabana ¹⁰
Solapersine	gal, glu, 2 xyl	<u>S. persicum</u>	Novuzov <u>et al.</u> ¹¹
Solatifoline	glu, gal, rham	<u>S. platanifolium</u>	Puri and Bhatmagar ¹²

^a glu = glucose, gal = galactose, rham = rhamnose, xyl = xylose

glycoalkaloids. Rapid procedures are available for quantitating specific glycoalkaloids. Solanum tuberosum tuber glycoalkaloids (α -solanine and α -chaconine) can be determined satisfactorily by reaction of antimony trichloride²¹ or formaldehyde-sulfuric acid²² with the base precipitated glycoalkaloids followed by colorimetric analysis. A rapid, semiquantitative analysis of potato glycoalkaloids using thin-layer chromatography (TLC) has recently been described.²³

Qualitative glycoalkaloid analysis is accomplished by either gas chromatography²⁴ or by TLC.²⁵ Unambiguous glycoalkaloid identification generally can be made by a combination of GC and TLC analysis.

Glycoalkaloids that differ by only minor modifications in the aglycone structure (e.g., solanidine or demissidine glycoalkaloids containing the same carbohydrate differ only by the degree of saturation between C-5 and C-6) may require more sophisticated techniques for separation such as argentation chromatography. A method has been described for distinguishing Δ^5 unsaturated glycoalkaloids from the corresponding saturated compounds based on their behavior to acid hydrolysis.^{26a}

BIOSYNTHESIS OF GLYCOALKALOIDS

The biosynthesis of the aglycones of Solanum species has been studied extensively; however, all the steps in the pathway have not been delineated. Biosynthesis proceeds from acetyl-CoA via the usual intermediates through cholesterol^{26b,27} to the various aglycones. The pathway from cholesterol to the aglycones has been partially inferred by the close relationship between steroid alkaloids and sapogenins in a given species, particularly with respect to the configuration at C-25. A hypothetical pathway for the formation of the solanidane, congestidine and spirosolane aglycones is shown in Figure 2. Although dormantinol and dormantinone have been isolated from plants that synthesize solanidine,²⁸ they have not been confirmed as intermediates by labeling experiments. The interconversion at C-22 has been postulated by Tschesche and Spindler.²⁹ The nitrogen apparently is derived from arginine.³⁰

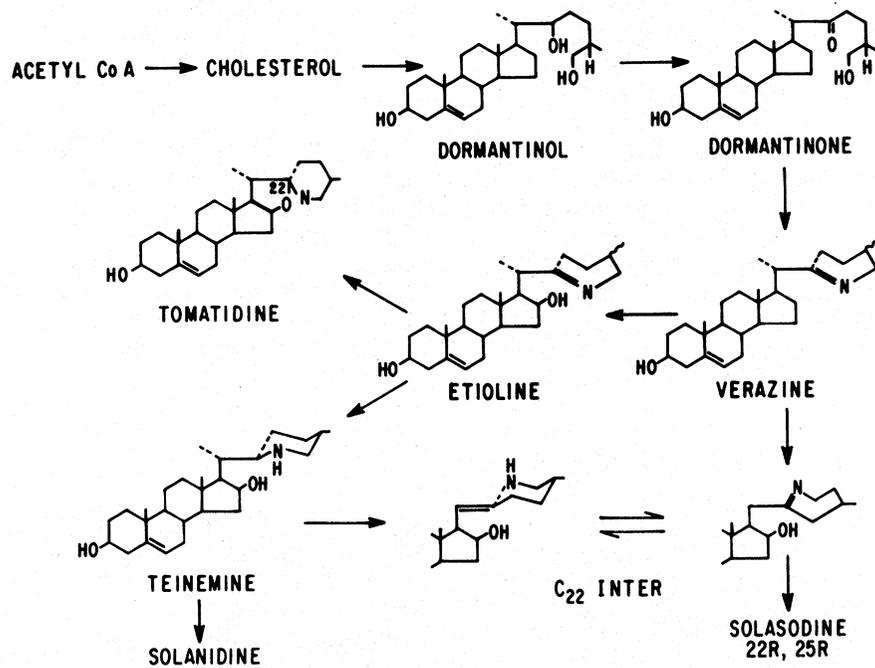


Figure 2. Aglycone biosynthetic pathway

TABLE 4
DISTRIBUTION OF GLYCOALKALOIDS IN POTATO
AND TOMATO PLANT

<u>Plant organ</u>	<u>% Glycoalkaloid (in dry tissue)</u>	
	<u>Potato^a</u>	<u>Tomato^b</u>
Flower	1.6 - 3.5 ^c	0.9 - 2.0
Leaf	0.5 - 0.6	.5 - 5.1
Stem	.03 - .06	.08 - 0.6
Sprouts	0.6 - 4.1	-
Root	0.1	0.2 - 0.6
Tuber	.006 - .04	-
Fruit	-	.087 - .036 ^d

a Lampitt et al.³⁶

b Roddick⁶

c Values include free solanidine

d Range decrease in levels during fruit ripening which fall to undetectable levels after 2-3 days beyond ripe (red) stage.

TABLE 5
GLYCOALKALOID DISTRIBUTION IN POTATO TUBER
(from Lampitt et al.³⁶)

<u>Tuber part</u>	<u>Part % of tuber</u>	<u>Total glycoalkaloids mg/100 dry wt</u>
Skin	2	64
Peel (skin & outer cortex)	11	68 - 75
Flesh	90	21

The glycosylation of solanidine^{31,32} and solasodine³³ has been demonstrated, although it has not been established whether the biosynthesis of the glycoalkaloid from the aglycone occurs through a step-wise addition of sugars similar to flavone glycoside synthesis.³⁴ Exogenous solanidine is metabolized in a step-wise manner to yield a diglucosyl solanidine,³⁵ which may be indicative of the endogenous glycosylation process.

GLYCOALKALOID DISTRIBUTION IN THE PLANT

Glycoalkaloids are usually found in all organs of the plant; the flowers contain the highest concentration of glycoalkaloids. In Table 4 the concentrations found in different organs of potato plants are compared with those reported for tomato. The values reported for potato were determined by Lampitt et al.³⁶ using the method of Rooke et al.;³⁷ the ranges of values reflect varietal and environmental effects on glycoalkaloid concentrations. The wide range of glycoalkaloid levels in tomatoes may also result from these effects and/or different methods of glycoalkaloid analysis. The distribution of glycoalkaloids in the potato tuber is shown in Table 5.

Glycoalkaloid concentration tends to be high in regions of high metabolic activity, such as meristems³⁸ and sprouts.^{32,36} Synthesis takes place predominantly in plant tops.³⁹ In both tomato³⁸ and potato,⁴⁰ grafting experiments have shown that glycoalkaloid synthesis in the shoot (leaves and stem) is independent of synthesis in the root. Tomato^{38,41} and potato³⁶ plant tissues metabolize glycoalkaloids and presumably change glycoalkaloid distribution within the plant as it matures. Glycoalkaloid metabolites have not been characterized; however, Sander⁴² suggested that tomatine may be utilized in lycopene synthesis. In the maturing potato plant, glycoalkaloid concentration increases in the flowers, stolon, and tubers while decreasing in other plant organs.³⁶

The intracellular distribution of tomatine has been determined by Roddick.⁴³ Organelles of pericarp tissue of green tomatoes were fractionated by centrifugation, and tomatine was found in the 105,000 g supernatant with a small amount in the microsomal fraction. Expressed juice of the fruit was also high in tomatine. These results

TABLE 6
TGA OF TUBERS FROM SELECTED SOLANUM SPECIES

Species	β -Chaconine	α -Chaconine	Glycoalkaloid α -Solanine	Solamarines ^a	Demissine	Tomatine
<u>S. ajanhuiri</u> ^b	3.5 ^c	39.0	57.3			
<u>S. curtilobum</u>		34.8	46.4	5.3	13.4	
<u>S. stenotomum</u>	5.5	69.8	24.7			
<u>S. juzepczukii</u>		14.0	37.8	7.7	40.4	
<u>S. acaule</u> 1 ^d					95.5	
2					62.1	30.9
3					88.2	11.6
4					64	34

- a Combined value for α - and β -solamarine.
b All species are cultivated except for S. acaule.
c Values represent percent of total glycoalkaloids.
d Four clones of species S. acaule were analyzed.

suggest that, in contrast to sterols which are found mainly in membrane fractions, glycoalkaloids accumulate in vacuoles and/or the soluble phase of the cytoplasm. Synthesis may occur in the microsomal organelles.

Genetic and environmental factors determine the TGA levels found in a particular plant. In Table 6, the TGA values for tubers of some tuber-bearing Solanum species are tabulated; these species are considered to have potential use as breeding stock.⁴⁴ The intraspecies as well as the interspecies variation is evident. Intraspecies variation is probably due to environmental factors. TGA levels increase with increased exposure to light,³² other factors such as temperature and soil condition may affect TGA to a lesser extent, but there is little data from which any correlations can be drawn. The cumulative effect of environment on TGA in a number of commercial varieties has been examined.^{45,46} Results for these varieties similar to those shown in Table 6 demonstrate that environmental factors can significantly alter the TGA levels. Analysis of these studies reveals that a "low TGA" variety (Irish Cobbler, average TGA = 6.2 mg/100 g FW) when grown in Alaska was higher in TGA level than a "high TGA" variety (Kennebec, average TGA = 9.7) grown in Texas; viz 10.9 vs 5.8.

Mechanical damage to potatoes not only increases TGA levels^{47,48} but may also cause qualitative changes in glycoalkaloid composition, such as the formation of α - and β -solamarine in slices of Kennebec tubers.⁴⁹ Damaged potatoes that are found in the market do not contain excessively high TGA levels.⁵⁰

BIOLOGICAL ACTIVITY

The function of glycoalkaloids in the plant is a controversial issue. Hegnauer⁵¹ coined the term "alcaloida imperfecta" to describe glycoalkaloids because he considered these compounds to be nitrogen derivatives of steroids and their nitrogen content and basicity accidental rather than essential characteristics. Fraenkel⁵² suggested a role for secondary metabolites, in general, based partly on Schreiber's⁵³ data for the pest repellent activity of Solanum glycoalkaloids. The finding that the species S. chacoense, which is resistant to the Colorado potato

beetle,⁵⁴ has high TGA levels and also contains the leptine glycoalkaloids,⁵⁵ which are highly repellent to the beetle in feeding tests,⁵⁶ rekindled interest in glycoalkaloids as significant factors for natural plant resistance to pests. In field experiments with S. chacoense x S. tuberosum hybrids, Schwarze was not able to correlate TGA levels with resistance to Colorado potato beetle.⁵⁷ Prior to the characterization of the leptines, Schreiber⁵³ hypothesized that the necessary structure for maximum repellency to the Colorado potato beetle was a saturated aglycone with a tetrasaccharide unit containing xylose. This hypothesis was based on glycoalkaloid feeding experiments. However, the leptines, which were subsequently recognized as probably the most active known glycoalkaloids toward the beetle do not have either of these structural features.

Tingey et al.⁵⁸ and Raman et al.⁵⁹ have presented convincing evidence that glycoalkaloids confer Solanum species resistance to the potato leafhopper (Empoasca fabae [Harris]) both in field experiments ($r = -0.75$, $P = 0.01$) and in feeding studies ($r = -0.86$, $P = 0.01$). These results support the earlier conclusions of Dahlman and Hibbs.⁶⁰

Although glycoalkaloids are toxic to many microorganisms, there appears to be no correlation between plant glycoalkaloid level and field resistance. Deahl et al.⁶¹ were not able to establish any relationship between glycoalkaloid levels and field resistance to late blight in 15 potato clones; similarly, Langcake et al.^{62a} found no correlation between glycoalkaloid levels in tomato roots and stems and resistance to Fusarium oxysporium f. lycopersici. However, Mohanakumain and coworkers found^{62b} that varieties of Lycopersicon pimpinellifolium resistant to Pseudomonas solanacearum had higher root tomatine levels than susceptible varieties.

Pathogens may have the ability to detoxify glycoalkaloids. Septoria lycopersici (leaf spot fungus of tomato) hydrolyzes tomatine to the trisaccharide β_2 -tomatine.⁶³ Solanidine was produced in minor amounts when solanine was incubated with P. infestans.⁶⁴

Glycoalkaloids may have a role as general, nonspecific protective agents against microbial or insect invasion. Tomatine has been shown to be effective against dermato-

mycetes particularly Trichophyton mentagrophytes⁶⁵ and fungotoxic levels of glycoalkaloids to the nonpathogen of potatoes, Helminthosporium carbonum, have been found in potato peels.⁶⁶ Arneson and Durbin suggested that high, localized tomatine concentration may inhibit fungal growth.⁶³ Although tomatine localization would not be reflected in TGA levels for the whole plant, this hypothesis has not received experimental confirmation. Even in the correlation of potato resistance to leafhopper⁵⁸ mentioned above, the authors realize that factors other than glycoalkaloid levels may be involved in plant resistance. Generally, the level of glycoalkaloids necessary to impart significant pest resistance would be too high to be considered as an acceptable means of resistance in food and feed crops (see below); however, these compounds may serve such a function in wild species in which they are present in considerable quantity.

TOXICITY OF GLYCOALKALOIDS

Glycoalkaloids have been suspected as the causative agent in potato poisoning even though there is little evidence in the literature to substantiate this claim. Zitnak⁷ has presented an excellent review of this subject from which one may conclude that the amount of glycoalkaloids lethal to humans is still an unanswered question; however, these compounds are responsible for undesirable effects such as vomiting, nausea, and diarrhea. The animal toxicity of pure glycoalkaloids has been determined only within the last 10 years. The LD₅₀ (oral, >1000 mg/kg) reflects the low absorption through the intestinal wall into the blood stream; 80% of radioactive α -chalonine is excreted within 48 hours.⁶⁹ Nishie et al.⁷⁰ determined the cardiotonic activity of six glycoalkaloids and one aglycone; the activity, in part, was correlatable to the number of sugars attached to the aglycone.

Renwick⁷¹ suggested that potato glycoalkaloids may be teratogens. Animal studies with pure glycoalkaloids have been negative;^{68,72,73} however, Keeler et al.⁷⁴ reported significant birth defects in the offspring of golden hamster females on diets containing potato sprout extracts.

CONCLUSIONS

Glycoalkaloids are still considered important starting compounds for steroidal hormone synthesis. The production of these compounds in cultured Solanum tissue is presently being investigated.⁷⁵ The only edible tissue that contains significant amounts of glycoalkaloids is potato tuber. The composition and concentration of glycoalkaloids found in commercial potatoes are acceptable at present; however, the use of new species should be carefully monitored for glycoalkaloids throughout the breeding program. The variety Lenape, which was derived, in part, from S. chacoense (a generally high TGA species containing other glycoalkaloids in addition to the normal tuber glycoalkaloids, α -solanine and α -chaconine), was withdrawn from production because of its high TGA content.¹ Research on the genetics of glycoalkaloid inheritance has been reported;^{76,77} and further studies of this type are necessary to determine to what extent glycoalkaloid inheritability is predictable. Improvement of the natural resistance of plants to pests and microorganisms has become an important goal today because of the environmental consequences of indiscriminate use of pesticides. Glycoalkaloids may contribute to natural resistance, but the toxicity of these compounds and the lack of knowledge of the efficacy of glycoalkaloids as natural pesticides mitigates against breeding programs designed to alter glycoalkaloid composition and content of plants at the present time. Continued research in pest resistance and heredity of glycoalkaloids in edible plants, particularly the potato, may make it possible to incorporate glycoalkaloids as part of a pest resistance program in the future.

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GLYCOALKALOIDS OF THE SOLANACEAE

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