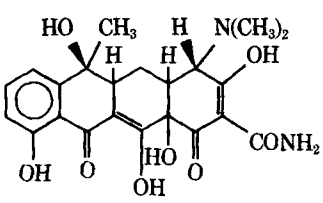
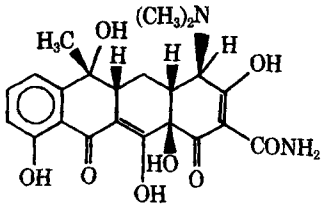
## Absolute Configuration of Tetracycline

During the past years, in approaching research in the area of tetracycline chemistry and obtaining reviews on manuscripts, some question has been raised as to the absolute configuration of tetracycline. This letter simply is a review of the primary literature in this area and, hopefully, will settle this controversy.

The structures of oxytetracycline[1] and chlortetracycline[2,3] were elucidated by chemical degradation early in the history of these antibiotics. The relative configurations at the asymmetric carbons were established chemically[3–10]; for 7-chlorotetracycline hydrochloride[11–13], oxytetracycline hydrochloride[14,15], anhydrotetracycline hydrobromide[16], and 2,5a-diacetyloxytetracycline[17], the configurations were approached by X-ray crystallography. This work establishing the configuration of the asymmetric centers has led to considerable confusion in the literature as to the exact absolute configuration because tetracycline and its related derivatives have been variously drawn as stereoisomers.



I



II

Some crystallographers have favored I[17] while others have favored II[11–16]. Since an anomalous scattering atom is not present in the tetracycline, the absolute configuration is indeterminate by X-ray crystallography. Furthermore, the apparent incongruities among the X-ray structures in the work done by NMR[18,19] and circular dichroism[20–24] have led to confusion among researchers.

The absolute configuration of the tetracyclines, however, was chemically determined[25] by degradation of chlortetracycline to a derivative that was comparable to a derivative prepared from atrolactinic acid, the absolute configuration of which is known. This work showed that I is, in fact, the correct absolute configuration of the tetracyclines.

It is hoped that this discussion will prevent further inconsistencies in the representation of the absolute configuration of the tetracyclines.

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## The Bloomin' Blossoms Have to Bloom to Be of Any Value

Until the FDA came forth with their regulations dealing with over-the-counter antacid drug products, industry had almost as many variations to demonstrate their products' acid-neutralizing power as there were antacids on the market. The end result was that no one could readily correlate the reported values, and the consumer was completely mystified as to what an antacid really should be.

In another field, dissolution test methods have promulgated proliferously in every direction possible during the past 15–20 years. The major purpose was to show that more of a given drug under the stated conditions, using the appropriately described apparatus, goes into solution faster than any of the competitive ones. This, of course, is good business strategy but very confusing and trying to those who attempt to interpret results from the different techniques. Being one of the many verbally battle-scarred victims, I felt great relief, and almost disbelief, that the USP finally took a firm stand on the dire need for a standard dissolution test.

We all like to be unique and very individualistic in the introduction of new and different approaches to an analytical problem because that is what makes the analysis of pharmaceuticals so intriguing and even exciting. However, there comes a time when a uniform approach, such as a compendium procedure, is a complete and unconditional necessity for the benefit of the one who really counts—the patient. I believe that the time is now for all of us in quality assurance to smoke a peace pipe and join the USP in its tremendous undertaking in putting sound scientific backing into a standard dissolution test and apparatus. *It can be done!*

Epilog: If the USP does not succeed, you know who will!

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