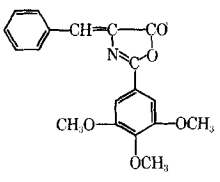
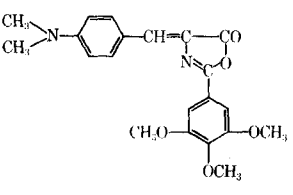
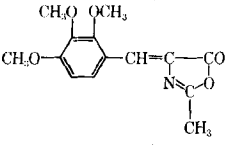
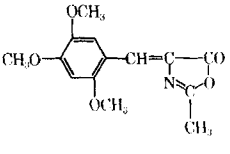
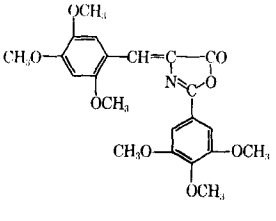
Infrared Studies of Some New Azlactones

By P. K. SHARMA and S. S. DAVE

The infrared spectra of five azlactones possessing the trimethoxy benzene structure are discussed, and an attempt is made to draw some structural inferences from the data reported.

FIVE AZLACTONES having the trimethoxy benzene structure were synthesized previously, and their central nervous system depressant actions have already been reported (1). The present communication deals with the infrared studies (Table I) and interpretation of those azlactones.

TABLE I—CHEMICAL STRUCTURE AND INFRARED ABSORPTION PEAKS OF SOME AZLACTONES

No.	Compd.	Structure	Absorption Peaks, cm.$^{-1}$	Intensity	Structural Inference
I	Azlactone of 3,4,5-trimethoxy benzoyl amino cinnamic acid		1750–1770	Strong	5-Membered cyclic ketone
			1240–1280	Variable	C=O (stretching)
			1650–1680	Variable	C=N (stretching)
			1130–1170	Weak	3,4,5-Trisubstituted aromatic ring
II	Azlactone of 3,4,5-trimethoxy benzoyl α-amino p-dimethyl-amino cinnamic acid		1770	Strong	5-Membered cyclic ketone
			1240	Strong	C=O stretching
			1680–1690	Strong	C=N (stretching)
			1130–1170	Weak	3,4,5-Trisubstituted aromatic ring
			1630	Variable	Dimethylamino group
III	Azlactone of α-acetyl amino 2,3,4-trimethoxy cinnamic acid		1750	Strong	5-Membered cyclic ketone
			1260	Variable	C=O (stretching)
			1260–1670	Variable	C=N (stretching)
			1000–1170	Strong	1,2,3-Trisubstituted aromatic ring
			1350–1370	Strong	C—CH_3 (CH deformation)
IV	Azlactone of α-acetyl amino 2,4,5-trimethoxy cinnamic acid		1750–1770	Strong	5-Membered cyclic ketone
			1260–1280	Variable	C=O (stretching)
			1650–1680	Variable	C=N (stretching)
			1020–1040	Strong	2,4,5-Trisubstituted aromatic ring
			1350	Strong	C—CH_3 (CH deformation)
V	Azlactone of 3,4,5-trimethoxy benzoyl α-amino 2,4,5 trimethoxy cinnamic acid		1730	Strong	5-Membered cyclic ketone
			1250	Variable	C=O (stretching)
			1660	Strong	C=N (stretching)
			1020	Strong	2,4,5-Trisubstituted aromatic ring
			1140	Weak	3,4,5-Trisubstituted aromatic ring

All of the five azlactones give absorption bands of variable intensity in the region of 1750 to 1770 cm.$^{-1}$. This peak suggests the existence of a 5-membered saturated cyclic ketone (2). To lend support to the above fact a C=O stretching mode appears between 1240 and 1280 cm.$^{-1}$ with strong intensity, indicating the presence of a cyclic anhydride type C—O—C structure. Moreover, since all of these compounds are azlactones, the presence of C=N in the structure is essential, as shown by the C=N stretching vibrations of variable intensity at frequencies 1680 and 1690 cm.$^{-1}$.

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Compound I gives the two characteristic bands at 1170 cm.$^{-1}$ and 1130 cm.$^{-1}$ of weaker intensity due to the presence of the 3,4,5-trisubstituted aromatic ring. Compound II shows in its spectra two bands at 1170 and 1130 cm.$^{-1}$ of the 3,4,5-trisubstituted aromatic ring, and the peak at 1630 cm.$^{-1}$ of weak intensity is due to the presence of the aromatic tertiary amine structure in the molecule. Compound III, being a 1,2,3-trisubstituted aromatic compound, shows absorption bands at 1000 and 1170 cm.$^{-1}$. Since there is a C-methyl group in the molecule, a peak at 1350 cm.$^{-1}$ due to CH deformation is observed. Compound IV, being a 2,4,5-trisubstituted derivative, gives absorption bands at 1000 and 1150 cm.$^{-1}$ and CH deformation for the C—CH_3 group at 1350 cm.$^{-1}$. With compound V, the bands of absorption at frequencies 1130 and 1000 cm.$^{-1}$ and 1170 to 1130 cm.$^{-1}$ clearly reveal that this compound contains two aromatic nuclei, both of which are trisubstituted.

REFERENCES

(1) Sharma, P. K., Menon, M. K., and Dandiya, P. C., *J. Pharm. Sci.*, **53**, 1055(1964).
(2) Bellamy, L., "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1958.

Synthesis and Chemotherapeutic Effects of Ethyl Bis-(2,2-dimethyl)-ethylenamido Phosphate. A Preliminary Report

By Z. F. CHMIELEWICZ, T. J. BARDOS, A. MUNSON, H. L. BABBITT, and J. L. AMBRUS

The title compound, a new analog of the experimental anticancer agent, AB-132, was synthesized and tested against a spectrum of transplanted animal tumors. It was found to have significant chemotherapeutic activity in all of the tumor systems studied. In these assays, the new compound was a much more effective antitumor agent than AB-132.

ETHYL BIS(2,2 - DIMETHYL - 1 - AZIRIDINYL)PHOSPHINYL CARBAMATE (AB-132) was synthesized in this laboratory several years ago (1). This compound, although only moderately effective against various transplanted tumors in rodents, nevertheless showed promising therapeutic activity in the clinical testing against various forms of human cancer, particularly, in conjunction with X-irradiation (2–5). In view of these results, it appeared of interest to synthesize the title compound (I), in which the urethan moiety of AB-132 is replaced by an ethoxy group.

RESULTS AND DISCUSSION

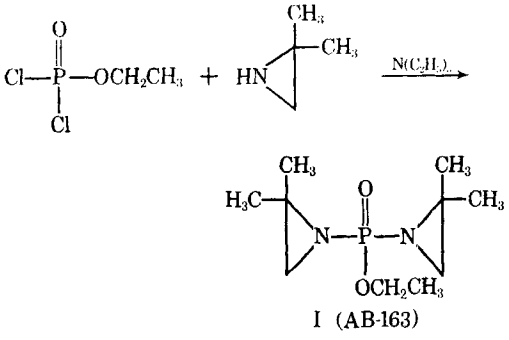
Ethyl bis(2,2-dimethyl)ethylenamido phosphate (I), designated as AB-163, was synthesized by the reaction of ethyl dichlorophosphate with 2,2-dimethylaziridine (in the presence of triethylamine) and purified by distillation under high vacuum, as described under *Experimental*. (Scheme I.)

The compound, a colorless, viscous oil, is readily soluble in water but, like other 2,2-dimethylaziridine derivatives, it undergoes rapid hydrolysis; it gradually decomposes even on exposure to air (humidity and carbon dioxide) and has to be stored in sealed containers. Its NMR spectrum shows the characteristic β-phosphorus splitting of the methylene protons, both in the aziridine rings and the ester group, and a singlet for the methyl substituents of the tertiary ring carbon.

In chemical alkylation studies, using 4-(*p*-nitrobenzyl)pyridine as a model nucleophile (6), AB-163 demonstrated a higher initial rate of alkylation compared to AB-132 (Fig. 1). Its higher chemical reactivity was paralleled by its greater toxicity. The LD_{50} of AB-163 in mice was 159 mg./Kg. (i.p.), in comparison to the 600 mg./Kg. LD_{50} value for AB-132.

The results of some of the antitumor studies are shown in Figs. 2–5. Details of the methods used in the animal assays will be published elsewhere.

Figure 2 shows the effects of various doses of AB-163 against Ehrlich ascites tumor in ICR/Ha mice. Treatment was started 24 hr. after inoculation, and the drug was administered intraperitoneally for 9 consecutive days. The animals were sacrificed on the 10th day and tumor cell counts were taken. Tumor inhibition was expressed as the per cent difference between the mean number of cells in the control group and the test group. At the optimal dose level (30 mg./Kg.), 95% inhibition was observed.



I (AB-163)

Scheme I

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