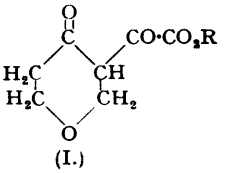
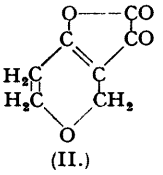
197. *Infra-red Spectroscopy and Structural Chemistry. Part II.* iso*Clavacin and Patulin.*

By John Frederick Grove.

The infra-red absorption spectra of *iso*clavacin and patulin have been examined, and the structures of these compounds are discussed in the light of these results and others obtained with suitable model substances.

Treatment of 3-ethoxalyltetrahydro-4-pyrone (I; R = Et) with a hydrogen halide in acetic acid in the presence of a small amount of water has been shown by Cohen *et al.* (B.P. 610,859; cf. *Chem. and Ind.*, 1949, 640) to yield a compound, $C_7H_6O_4$, m. p. 87°, isomeric with the antibacterial mould product patulin.


(I.)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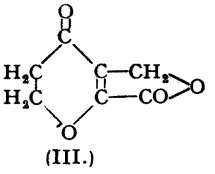
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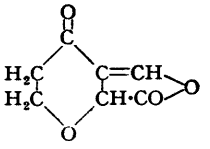
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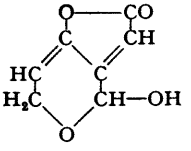
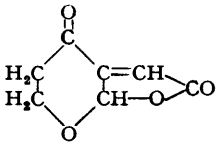
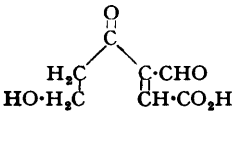

(V.)

Two possible structures were considered for this isomer : (II), derived from (I) by enolisation and lactonisation, and (III), in which, after initial opening of the tetrahydropyrone ring of (I), enolisation of the β-diketone system has occurred in the opposite direction and has been followed by lactonisation and ring closure to the dihydropyrone. The chemical evidence recently reported by Cohen (*Chem. and Ind., loc. cit.*) favours (III); moreover, the compound is stated to be identical with that obtained by Puetzer, Nield, and Barry (*Science*, 1945, **101**, 307; *J. Amer. Chem. Soc.*, 1945, **67**, 832) by the cyclisation of α-keto-β-β′-methoxypropionylbutyrolactone with sulphuric acid and called *iso*clavacin. The possible conversion of (I) into (III) by the above mechanism suggests that we are dealing with a system of high mobility, in which the determination of structure by the use of chemical reagents and by observation of chemical reactions may be open to criticism. It is perhaps relevant that the structural formulæ, (IV), (V), and (VI), proposed for patulin by Raistrick, Birkinshaw, Michael, and Bracken (*Lancet*, 1943, **245**, 625; see also Bergel, Morrison, Moss, and Rinderknecht, *J.*, 1944, 415), Woodward

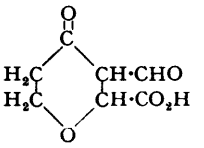
and Singh (*J. Amer. Chem. Soc.*, 1949, **71**, 758), and Engel, Brzeski, and Plattner (*Helv. Chim. Acta*, 1949, **32**, 1166, 1752) respectively, may all be derived from β-formyl-β-β′-hydroxypropionyl-



(VI.)



(VII.)



(VII*a*.)

acrylic acid (VII) by the elimination of a molecule of water. [Woodward and Singh (*Experientia*, 1950, **6**, 238) have recently discussed this aspect of the problem more fully.] The formation of (IV) involves the cyclic form (VII*a*). The cyclisation of $\Delta^{\gamma\delta}$-carboxylic acids to the corresponding saturated lactones is well known; similar phenomena may occur with unsaturated alcohols in which the double bond is suitably polarised, and there is some evidence that certain substituted allyl alcohols exist in cyclic form (Hills, Kenyon, and Phillips, *Chem. and Ind.*, 1933, **52**, 660).

Accordingly, it seemed desirable to investigate physical methods capable of distinguishing between (II) and (III), which did not involve solution of the compound in a hydrolytic solvent; infra-red absorption spectroscopy was an obvious choice.

The published ultra-violet absorption data for *iso*clavacin ($\lambda_{max.}$ = 276 mμ.; log ε = 3·97) strongly suggest the presence of a system consisting of three conjugated chromophores, and favour (III). Structure (IV) for patulin ($\lambda_{max.}$ = 277 mμ.; log ε = 4·22) is also unlikely on the ultra-violet absorption evidence.

TABLE I.

Structure.	Grouping.	Predicted frequency (cm.$^{-1}$).
(II)	$\Delta^{\beta\gamma}$ five-membered ring lactone C=O	1800
	$\Delta^{\alpha\beta}$ five-membered ring ketone C=O	1715
(III)	$\Delta^{\alpha\beta}$ five-membered ring lactone C=O	1750
	$\Delta^{\alpha\beta}$ six-membered ring ketone C=O	1680
(IV)	$\Delta^{\beta\gamma}$ five-membered ring lactone C=O	1800
	$\Delta^{\alpha\beta}$ six-membered ring ketone C=O	1680
(V)	OH	3200—3450
	$\Delta^{\alpha\beta}\Delta^{\gamma\delta}$ (exocyclic) five-membered ring lactone C=O	1770 *
(VI)	$\Delta^{\alpha\beta}$ five-membered ring lactone C=O	1750
	$\Delta^{\alpha\beta}$ six-membered ring ketone C=O	1680

* The nearest available model for this lactone is 3-methylenephthalide (Grove and Willis, preceding paper) which absorbs at 1780 cm.$^{-1}$. The figure 1770 cm.$^{-1}$ is obtained by subtracting 10 cm.$^{-1}$ to allow for the superior conjugating effect of the ethylenic C=C as compared with the benzene nucleus.

Recent work on the characteristic stretching vibrations of carbonyl groups (summarised in Part I, preceding paper) has enabled reliable correlations to be made between the C=O absorption frequency and structure. The C=O and OH stretching frequencies, predicted for compounds of structures (II)—(VI) by use of these correlation rules, are included in Table I and the values actually observed for patulin and *iso*clavacin in Table II.

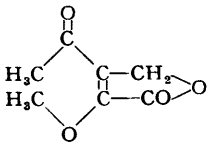
TABLE II.

	Frequency (cm.$^{-1}$).			Frequency (cm.$^{-1}$).	
	C=O.	OH.		C=O.	OH.
*iso*Clavacin	1768, 1688	—	Patulin	1768, 1745 *	3390

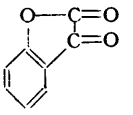
* " Shoulder " to main absorption band.

The high-frequency band associated with the βγ-unsaturated five-membered lactone ring of formula II is not observed, and the tables provide additional support for the view that *iso*clavacin is (III), although the agreement between the observed frequencies and those predicted for this structure is only fair. However, the total shift associated with the conjugating effect of an ethylenic double bond was taken into account in calculating the absorption frequencies of both C=O groups of (III); it would be more reasonable to assume that the C=C which is common to the C=O groups would not exert its full effect on both, and the lactone C=O absorption does in fact fall closer to that normally associated with an unconjugated five-membered ring lactone (1770 cm.$^{-1}$).

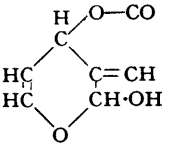
The results for patulin favour structure (V) and are in good agreement with those published by Woodward and Singh (*loc. cit.*). In particular, the strong, alcoholic OH absorption at



(VIII.)



(IX.)



(X.)

3390 cm.$^{-1}$ provides additional evidence.* It is not easy to account for the shoulder at 1745 cm.$^{-1}$ but taken in conjunction with another weak band at 1680 cm.$^{-1}$, which may be due to C=O or C=C, it may indicate the presence of a small percentage of another structure such as (X). Alternatively it is possible that there is intermolecular hydrogen bonding between C=O and OH groups of the type discussed in the preceding paper, involving a small proportion of the molecules only, and that this type of dimerisation persists in solution and therefore appears in the solution spectra obtained by Woodward and Singh.

Additional evidence in support of (III) for *iso*clavacin has been obtained from examination of the model compounds, β-acetyl-α-methoxy-$\Delta^{\alpha\beta}$-butenolide (VIII) and coumaran-2 : 3-dione (IX) (cf. Table III).

TABLE III.

	Grouping.	C=O Stretching frequency, Predicted.	Found.
(VIII)	$\Delta^{\alpha\beta}$ five-membered ring lactone C=O	1750	1770
	$\Delta^{\alpha\beta}$ acyclic ketone C=O	1670	1670
(IX)	lactone C=O } see below	1810	1833
	ketone C=O } see below	1730	1740

The spectrum of (VIII) was practically identical with that of *iso*clavacin in the double-bond stretching region. The arguments used above in the case of *iso*clavacin may be applied to account for the apparent discrepancy between the observed and predicted values of the lactone ring C=O vibration.

In attempting to predict the C=O frequencies for coumaran-2 : 3-dione, 10 cm.$^{-1}$ have been added to those estimated for (II) to allow for the weaker conjugating effect of the benzene nucleus compared with that of an ethylenic double bond. The observed frequencies are appreciably higher, perhaps because of the greater strain in the heterocylic ring or more probably because of some electronic or interaction effect analogous to that observed in pyruvic acid and methyl pyruvate. In the latter compound the ketone C=O absorption is shifted to a frequency (1745 cm.$^{-1}$) some 30 cm.$^{-1}$ higher than the normal value (1715 cm.$^{-1}$) for an unconjugated acyclic ketone (cf. Randall, Fowler, Fuson, and Dangl, " Infra-red Determination of Organic Structures," van Nostrand, New York, 1949, p. 166).

EXPERIMENTAL.

Infra-red Spectra.—These were obtained using the modified Hilger D 209 instrument described in the preceding paper. β-Acetyl-α-methoxy-$\Delta^{\alpha\beta}$-butenolide was examined as a liquid, the other compounds as powders in " Nujol " suspension.

Materials.—Authentic specimens of patulin, m. p. 111°, and *iso*clavacin, m. p. 87°, were kindly supplied by Dr. A. Cohen. Coumaran-2 : 3-dione, yellow needles, m. p. 132°, was purified by crystallisation from benzene–light petroleum.

β-Acetyl-α-methoxy-$\Delta^{\alpha\beta}$-butenolide. This was obtained from Dr. A. L. Morrison who prepared it in the following manner :

β-Acetyl-α-ketobutyrolactone (4·12 g.) was added to an excess of diazomethane in ether, and the ether and excess of diazomethane were distilled off, leaving the *lactone* as an oil, b. p. 130°/13 mm. [$\lambda_{max.}$ (in methanol) = 270 mμ.; log ε = 4·08] [Found : OMe, 20·1%; equiv. (by titration), 156. $C_7H_8O_4$ requires OMe, 20·0%; equiv., 156].

I am indebted to Dr. F. Bergel for many interesting discussions on this work, to Dr. A. Cohen and Dr. A. L. Morrison, Research Department, Roche Products Ltd., for gifts of chemicals, and to Mr. H. A. Willis and the Directors of Imperial Chemical Industries Limited, Plastics Division, for the use of infra-red facilities.

IMPERIAL CHEMICAL INDUSTIRES LIMITED, BUTTERWICK RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS. [*Received, November 3rd*, 1950.]

* While this paper was in preparation, Dauben and Weisenborn (*J. Amer. Chem. Soc.*, 1949, **71**, 3853) reported the presence of an OH band in the patulin spectrum.