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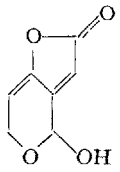
STUDIORUM PROGRESSUS

The Structure of Patulin[1]

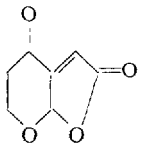
By R. B. WOODWARD and GURBAKHSH SINGH, Cambridge (U.S.A.)[2]

Patulin is a mold metabolic product of the composition $C_7H_6O_4$. *It is produced by a large number of microorganisms, and possesses marked antibiotic and antifungal properties. In spite of the small size of the molecule of the antibiotic, its chemistry has turned out to be extraordinarily intricate. In 1943, a structure was proposed for the substance by* RAISTRICK, et al. *The expression deduced at that time has been generally accepted, although the possibility of the existence of patulin in tautomeric modifications of the original structure has been considered. It has long been our view that a more radical alteration of the early proposal was necessary. Recently, experimental confirmation of the necessity for such changes has been brought forward in Zürich and in Cambridge.*

In a recent letter, COHEN[3] in referring to structures proposed for patulin by us (I)[4], and by ENGEL, BRZESKI, and PLATTNER (II)[5], calls attention to the necessity



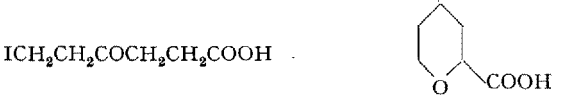
I



II

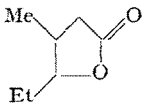
of showing that any structure for the antibiotic is consistent with the extensive degradative work of RAISTRICK *et al.*[6] and BERGEL *et al.*[7] (The work of the NAUTA group[8] also deserves mention.) These remarks prompt us to record our views in that direction, the more so since our structural proposal was of course based in the first instance on the elegant experiments to which COHEN refers. It will be understood that in our earlier communication, of strictly prescribed length, we had no choice but to focus our attention on the new results which we were able to bring forward in support of our conclusions.

RAISTRICK *et al.*[9] obtained ε-iodo-γ-ketohexoic acid (III) by treating patulin with hydriodic acid. It was further shown that patulin was converted by hot dilute sulfuric acid to tetrahydrocomanic acid (IV) and formic acid. When hydrogenated patulin was treated with phosphorus and hydriodic acid, β-methylcaprolactone (V) and β-methylcaproic acid (VI) were formed. We consider it unnecessary to labor the

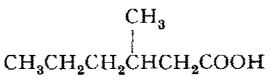


III

IV

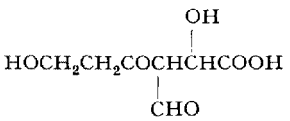


V

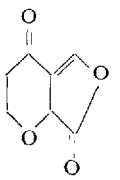


VI

point that these results prove rigorously only *that patulin is convertible in aqueous media, in the presence of acidic catalysts, to (VII), or an equivalent species.* A great many



VII

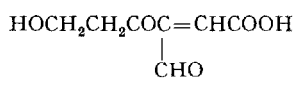


VIII

structures for patulin meet this requirement, among them, (I), (II), and the original proposal (III) of the RAISTRICK group.

We turn now to a consideration of the significance of the isolation by NAUTA *et al.*[1] of 2,3-diketopentane (IX) and carbon dioxide as products of the vigorous hydrolysis of patulin by hydrochloric acid. This result is readily explicable if it be assumed that the patulin molecule contains a double bond conjugated with the (potential) carboxyl group known to be present, i. e. that patulin is a lactone derived from (X). The hydration

IX



X

of the double bond of (X) will be expected to proceed mainly in the direction of the formation of (VII); on the other hand, activation for addition in the opposite sense is present in the —COO— group, and reaction in this alternate direction may be favored in the patulin molecule itself through modification of the carbonyl group at the other end of the double bond. Thus, to the extent that hydration of the double linkage precedes cleavage of the lactone ring, we may expect (XI) to be formed when patulin is treated with aqueous acids. Now,

[1] The manuscript is in the hands of the editor since October 14, 1949.

[2] Converse Memorial Laboratory, Harvard University.

[3] A. COHEN, Chemistry and Industry *37*, 640 (1949).

[4] R. B. WOODWARD and G. SINGH, J. Amer. Chem. Soc. *71*, 758 (1949).

[5] B. G. ENGEL, W. BRZESKI, and PL. A. PLATTNER, Helv. chim. acta *32*, 1166 (1949); *32*, 1752 (1949).

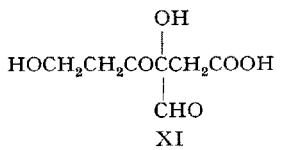
[6] H. RAISTRICK, J. H. BIRKENSHAW, S. E. MICHAEL, and A. BRACKEN, Lancet *245*, 625 (1943).

[7] F. BERGEL, A. L. MORRISON, A. R. MOSS, and H. RINDERKNECHT, J. Chem. Soc. 415 (1944).

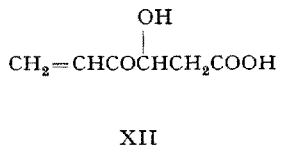
[8] W. TH. NAUTA, H. K. OOSTEHUIS, A. C. VAN DER LINDEN, P. VAN DUYN, and J. W. DIENSKE, Rec. Trav. chim. *65*, 865 (1946).

[9] H. RAISTRICK, J. H. BIRKENSHAW, S. E. MICHAEL, and A. BRACKEN, Lancet *245*, 625 (1943).

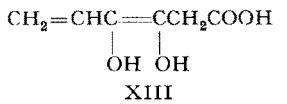
[1] W. TH. NAUTA, H. K. OOSTEHUIS, A. C. VAN DER LINDEN, P. VAN DUYN, and J. W. DIENSKE, Rec. Trav. chim. *65*, 865 (1946).



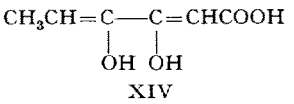
XI



XII



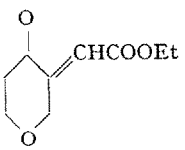
XIII



XIV

if the formyl group of (XI) is cleaved in the normal fashion, and the hydroxyl group β to the carbonyl function is lost, (XII) will be formed. A shift of the double bond system in the corresponding enol (XIII) into conjugation with the carboxyl group will lead to (XIV), from which the observed 2,3-diketopentane (IX) and carbon dioxide result by obvious processes.

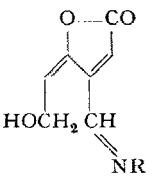
The two lactones derivable from (X) are (I) and (II). Of these, we favor (I), for these reasons: (i) there is strong positive evidence for the presence of a *bona fide* hydroxyl group in the patulin molecule in the ready formation of numerous acyl derivatives, and of a methyl ether, in the complete identity of the ultraviolet absorption spectra of patulin and its acyl derivatives, and in the presence of a strong OH band in the infra-red spectrum of patulin. (ii) The infra-red spectrum of



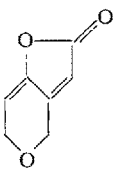
XV

patulin has no strong band at *ca.* 6μ; such a band should be present in the spectrum of (II), which contains the system CO—C=C. (iii) The ultraviolet spectrum of patulin is incompatible with the structure (II); thus, the ester (XV), containing an absorbing system closely comparable to that of (II), has $\lambda max.=240$ mμ[1]. (It should be pointed out that the ultraviolet data alone were sufficient to render the structure (VIII) for patulin unacceptable.) (iv) Addition of water to the double bond of (II) in the sense described above as necessary to encompass the formation of 2,3-diketopentane is relatively unlikely. (v) (II) contains the system —CH_2CO—, but patulin does not form a benzylidene derivative[2]. (vi) Patulin, though derived from natural sources, is optically inactive; while (I), as a hemiacetal, would be expected to racemize rapidly in solution (cf. the mutarotation of sugars, etc.), an active form of (II) would be expected to be configurationally stable. In this general connection we may call attention to the fact that the acceptance of the structure (I) implies that the various carbonyl derivatives of patulin are derived from the potential carbonyl group which in (I) is present as the above-mentioned hemiacetal function. Thus the oxime, and the phenylhydrazones of patulin may be represented as (XVI); this view is in accord with the fact that the acyl derivatives of patulin give the same compounds with carbonyl reagents as does patulin itself. (vii) Finally, the ultraviolet spectrum and the infra-red spectrum, in the double bond region, of the model lactone (XVII) prepared by us[1] are substantially identical with the corresponding properties of patulin itself.

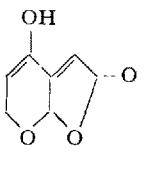
Some, but not all, of the above-mentioned defects of (II) do not obtain if it be assumed that such a molecule would exist *entirely* in the enolic form (XVIII). We see



XVI



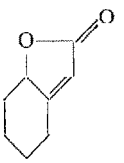
XVII



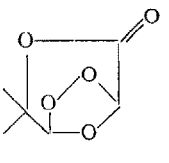
XVIII

no grounds for the acceptance of such an assumption, and beyond that, our measurements of the infra-red spectrum of patulin fail to reveal the *strong* bond at 6·0—6·1 μ which would be expected to appear in the spectrum of (XVIII), as a consequence of the presence in the molecule of the system C=C—O—R (R=H *or* alkyl)[2].

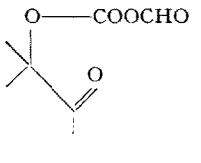
It remains to consider the structure (I) for patulin in the light of the extensive and careful experiments of the



XIX



XX



XXI

BERGEL group[3]. The formation of glyoxal from (I) on ozonization is readily understandable[4]; it may be noted that NAUTA *et al.* obtained glycolic aldehyde, as well as glyoxal[5]. The fact that no glyoxylic acid was observed as an ozonization product deserves comment. Attention may be called to the work of COCKER and HORNSBY[6], who looked for, and did not find, glyoxylic acid among the ozonization products from the lactone (XIX). It may be suggested that the ozonide of patulin suffers rearrangement in the sense (XX)→(XXI); this process would lead to the formation of formic acid and *carbon dioxide*, both of which were observed. The formation from patulin, by perhydrogenation, etc., of β-*n*-propylbutyrolactone (XXII) does not require explication; a number of paths are available, and the result in the main serves only to confirm the already well-established carbon skeleton of the antibiotic. The action of ethanolic hydrogen chloride on (I) may be expected to lead to the *pseudo* ester (XXIII).

[1] Unpublished observations from our Laboratory.

[2] F. BERGEL, A. L. MORRISON, A. R. MOSS, and H. RINDERKNECHT, J. Chem. Soc. 415 (1944). – W. TH. NAUTA, H. K. OOSTEHUIS, A. C. VAN DER LINDEN, P. VAN DUYN, and J. W. DIENSKE, Rec. Trav. chim. *65*, 865 (1946). – But compare NAUTA *et al.*, *loc. cit.*, p. 873, who state that patulin gives a benzal derivative. The substance was not analysed or otherwise characterized, and it seems very probable, from the method used, that the product obtained by the Dutch workers was chlorodesoxypatulinic acid.

[1] R. B. WOODWARD and G. SINGH, J. Amer. Chem. Soc. *71*, 758 (1949).

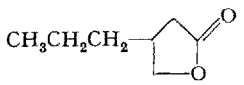
[2] Unpublished observations from our Laboratory on the spectra of dihydropyrane, and other enol ethers.

[3] F. BERGEL, A. L. MORRISON, A. R. MOSS, and H. RINDERKNECHT, J. Chem. Soc. 415 (1944).

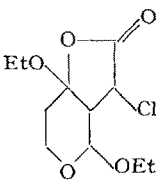
[4] Cf. BERGEL, *et al.*, *loc. cit.*, p. 417.

[5] W. TH. NAUTA, H. K. OOSTERHUIS, A. C. VAN DER LINDEN, P. VAN DUYN, and J. W. DIENSKE, Rec. trav. chim. *65*, 865 (1946).

[6] W. COCKER and S. HORNSBY, J. Chem. Soc. 1157 (1947).

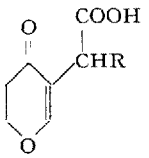


XXII

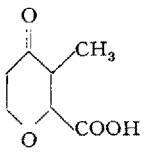


XXIII

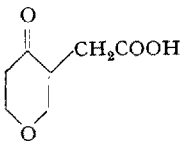
The expression is a satisfactory one in all respects for the product $C_{11}H_{17}O_5Cl$ obtained by the BERGEL group. This view further implies that the chloro-acid, $C_7H_7O_4Cl$, (now known as chlorodesoxypatulinic acid[1]) obtained by the action of warm dilute sulfuric acid on (XXIII), has the structure (XXIV: R = Cl) and that the acid $C_7H_{10}O_4$, obtained by reduction of the chloroacid, and formulated by BERGEL *et al.* as (XXV), is in fact the tetrahydro-γ-pyrone-3-acetic acid (XXVI). The latter de-



XXIV



XXV



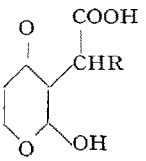
XXVI

duction has been rigorously confirmed by experiments in Zürich[1] and Cambridge[2]. (It may be noted that strong evidence against the structure (XXV) for the acid $C_7H_{10}O_4$ was long since available in the observation by the BERGEL group that the substance was transformed by hydriodic acid into a *diiodo*-acid $C_7H_{10}O_3I_2$; it can hardly be doubted that (XXV) in this reaction would suffer reductive cleavage of the C—O link α to the carboxyl group, with formation of a *monoiodo*-acid $C_7H_{11}O_3I$).

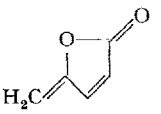
The very valuable and interesting recent degradative studies of the PLATTNER group[1] likewise are readily interpretable in terms of the structure (I). Thus, patulin was converted directly to the chloro-acid (XXIV: R = Cl) by the action of hydrogen chloride in *moist* ether. Further, the direct hydrogenation of patulin in *aqueous* media led to the formation of the acid (XXIV: R = H). Although a number of alternate reaction paths for these processes present themselves, the simplest involves the addition of hydrogen chloride, in the first case, or hydrogen, in the second, to the double bond which remains after hydrolytic cleavage of the lactone ring. These changes will lead to (XXVII: R = Cl *or* H), from which by obvious processes the observed products may be derived.

[1] B. G. ENGEL, W. BRZESKI, and PL. A. PLATTNER, Helv. chim. acta *32*, 1166 (1949); *id.*, *ib.* *32*, 1752 (1949).

[2] R. B. WOODWARD and G. SINGH, J. Amer. Chem. Soc. *71*, 758, (1949).



XXVII



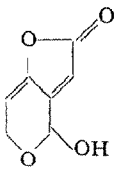
XXVIII

In view of the fact that interest in patulin first devolved from its powerful antibiotic properties, it is perhaps pertinent to point out that the structure (I) bears a strong resemblance to that of protoanemonin (XXVIII), whose antibiotic properties are well-known[1].

Few known substances contain as many reactive groupings, combined so compactly, as does patulin, and the chemistry of the antibiotic is more than ordinarily intricate. But the structure (I) is an eminently satisfactory vehicle for the interpretation of all the known facets of the chemistry of patulin, and in our view it is unquestionably correct.

Zusammenfassung

Die Erwägungen, welche die Autoren zu der Struktur I für Patulin führten, werden kurz beschrieben, und es wird gezeigt, daß das chemische Verhalten des Naturstoffes in jeder Hinsicht durch diese Strukturformel zu erklären ist.



I

[1] B. C. SEEGAL and M. HOLDEN, Science *101*, 413 (1945). – H. BAER, M. HOLDEN, and B. C. SEEGAL, J. Biol. Chem. *162*, 65 (1946).

Congrès

FRANCE

Le Congrès international de Microscopie électronique

aura lieu à Paris du 14 au 22 septembre 1950

Pour tous renseignements on peut s'adresser au Dr C.-A. BAUD, Laboratoire de morphologie ultrastructurale et fonctionnelle, rue Ecole de Médecine, 20, Genève.