Tetrahedron. 1961, Vol. 16, pp. 185 to 191. Pergamon Press Ltd. Printed in Northern Ireland

AN ACETYLENIC APPROACH TO PATULIN DERIVATIVES*

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(*Received* 18 *March* 1961)

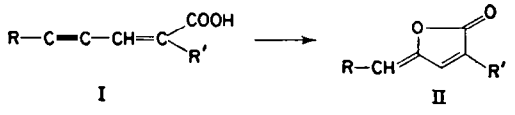
Abstract—A new route for the preparation of patulin-oxime, and other carbonyl derivatives of patulin, in a substantial yield, starting from acetylenic compounds, is described.

Chemical and theoretical evidence is presented for stereomutation in the preparation of carbonyl derivatives from patulin.

AMONG metabolites of micro-organisms, patulin[1] occupies a unique position. While its structure was a matter of great controversy, until Woodward and Singh[2a] proposed the correct structure, no serious efforts have been made to synthesize it. In the synthesis reported by the authors[2b] no experimental details are given and the yields reported are rather discouraging.

The results obtained in an attempted synthesis of patulin, taking advantage of the great versatility of acetylene compounds, are here described.

Recently, the easy isomerization of substituted propargylidenmalonic[3] (I, R′ = CO_2H) and *cis*-propargylidenacetic acids[4] (I, R′ = H) to γ-methylenbutenolides (II), has been reported.



I II

This reaction has been widely used to prepare synthetic methylenbutenolides, with biological activity,[5] and seemed a promising route for the preparation of natural methylenbutenolides, such as protoanemonin (II, R and R′ = H) and patulin (V). Actually, protoanemonin seems to be spontaneously formed when *cis*-pent-4-yn-2-enol is oxidized to the corresponding acid[4b] (I, R and R′ = H).

* A preliminary note was presented at the XXXII International Congress of Industrial Chemistry, held in Barcelona, October 1960.

[1] See references collected in W. Karrer, *Konstitution und Vorkommen der organischen Pflanzenstoffe* p. 448. Birkhäuser Verlag, Basel und Stuttgart (1958); E. H. Rodd, *Chemistry of Carbon Compounds* IV B; p. 837. Elsevier, New York (1959).

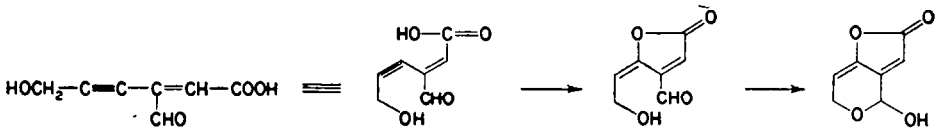
[2a] R. B. Woodward and G. Singh, *J. Amer. Chem. Soc.* **71**, 758 (1949); *Experientia* **6**, 238 (1950); *Nature, Lond.* **165**, 928 (1950); [2b] *J. Amer. Chem. Soc.* **72**, 1428 (1950).

[3] J. Castañer and J. Pascual, *J. Chem. Soc.* 3962 (1958).

[4a] P. K. Christensen, *Acta Chem. Scand.* **11**, 5782 (1957); P. K. Christensen, N. A. Sørensen, I. Bell, E. R. H. Jones and M. C. Whiting, *Festschrift Arthur Stoll* p. 545. Birkhäuser, Basel (1957); [4b] I. Bell, E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.* 1313 (1958).

[5] J. Pascual, J. Castells and F. Serratosa, *Memoria Ayuda Fundación Juan March Grupo* III. 1958–1960.

Similarly, patulin could be hypothetically derived from an open-chain *en-yne*, such as III, according to the sequence:

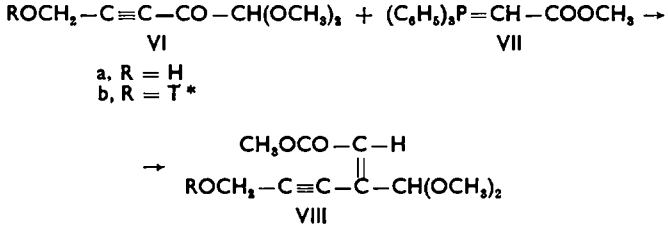


III IV V

but, if "few known substances contain as many reactive groupings, combined so compactly, as does patulin",[2a] its hypothetic progenitor (III) shows a panoramic view of the aliphatic chemistry, and ought to be prepared with all its groups conveniently protected to hydrolyse them selectively and control its reactivity.

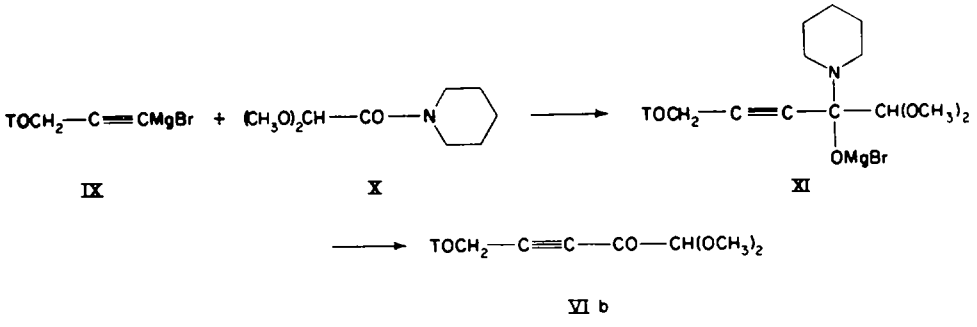
The stereochemistry of the synthesis requires a *cis*-configuration of the carboxyl group to the triple bond in structure III, and the same *cis*-configuration in the newly formed double bond of IV. It was thought that both requirements would be easily met, even if the nucleophilic addition of the carboxyl group to triple bond were *trans*, as has been suggested,[3] since an $\alpha, \beta, \gamma, \delta$-unsaturated carbonylic system, as is present in IV, should have a low energy of isomerization.

The analysis of structure III suggested a Wittig reaction, between the acetylenic ketoacetal (VI) and the well known carbomethoxymethylen-triphenylphosphorane (VII), to synthesize the key intermediate (VIII).



VI (a, R = H; b, R = T*) + VII → VIII

For the preparation of the acetylenic ketoacetal (VI), a synthesis of α-ketoacetals by Wohl and Lange,[6] applied to acetylenic Grignard derivatives, was undertaken. Thus, when the Grignard derivative of propargyl alcohol—as tetrahydropyranyl ether (IX)—is allowed to react with N-dimethoxyacetyl-piperidine (X), the acetylenic ketoacetal (VI b) is obtained.



IX X XI → VI b

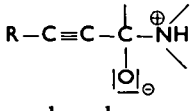
* T refers to the tetrahydropyranyl group.

[6] A. Wohl and M. Lange, *Chem. Ber.* **41**, 3612 (1908).

The intermediate complex (XI) resists further reaction and no tertiary alcohol is formed, even with an excess of Grignard reagent, and by using the usual addition technique.

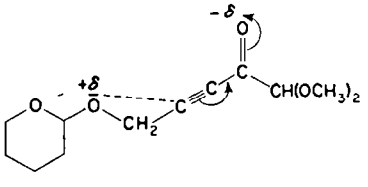
Although Wohl and Lange,[6] and more recently Wright,[7] hydrolyse the intermediate complex by means of a very weak acid, such as ammonium chloride, in the present case so mild a treatment leads to a product, which on distillation affords only starting materials together with considerable amounts of resins. The intermediate is even stable in aqueous solution of tartaric acid. However, hydrolysis with dilute sulfuric acid leads, in fair yields, to the acetylenic ketoacetal (VI b), easily distillable at high vacuum, and identified by its infra-red bands at 2212 (m) and at 1689 (s) cm^{-1} (in Cl_4C) (a very weak band at 1647 cm^{-1} is also present, even after redistillation, indicating the presence of some amide (X) as impurity). These results parallel those of Jones *et al.*[8] in the synthesis of acetylenic aldehydes from dimethylformamide, but the presence of acid sensitive acetal groupings in the ketoacetal (VI b), necessitates an adjustment in the strength of the acid hydrolysis.

Since the intermediate complexes from N-disubstituted amides and either alkyl, or arylmagnesium halides are successfully hydrolysed with weak acids,[6,7,9] and high yields of carbonyl compounds are obtained, the acetylenic triple bond must be responsible for the slow rate of hydrolysis, and intermediates of the type must be



postulated. They can give either carbonyl compound (probably through imonium salts), or starting materials, depending upon the acid hydrolysis conditions and the nature of acetylenic component.*

The stability of the tetrahydropyranyl grouping, usually so sensitive to mineral acids, in the sequence leading to the acetylenic ketoacetal (VI b), deserves comment. It can be related to a conjugation of π-p type, across a saturated carbon atom, between the ether bridge and the conjugated system, the ether oxygen atom becoming sufficiently electron-poor to repel the attack of a proton (XII). Similar interactions have been reported, and correlated with the ultra-violet absorption.[10]



XII

The condensation of the acetylenic ketoacetal (VI b) with carbonmethoxymethylen-triphenylphosphorane (VII), affords the key intermediate (VIII b), as anticipated.

* The results and the interpretation of infra-red data in similar cases, favors such supposition, and it will be discussed elsewhere.

[7] J. B. Wright, *J. Amer. Chem. Soc.* **77**, 4883, (1955).
[8] E. R. H. Jones, L. Skattebøl and M. C. Whiting, *J. Chem. Soc.* 1054 (1958).
[9] J. Sicé, *J. Amer. Chem. Soc.* **75**, 3697 (1953).
[10] *Ann. Reports* **51**, 167 (1954).

Ester VIII b is a mixture of *cis* and *trans* isomers, the former being predominant, as could be predicted by the relative volume of the groups involved. As a trisubstituted olefinic system, correlations in the infra-red are difficult and the characteristic splitting of the C=O stretching of esters *cis*-R—C≡C—CH=CH—CO_2Me[11] is not clearly observed. Bands at 2212 (w), 1733 (s), 1715 (sh), and at 1623 (m) cm^{-1} are present, in carbon tetrachloride as a solvent.

The mixture of esters is hydrolysed in alkaline medium to the parent acids (XIII), neither being isolated in a pure condition. The *cis*-acid spontaneously cyclizes to butenolide (XIV), the reaction being catalysed by traces of Ag.† The *trans*-acid is removed from the mixture by sodium bicarbonate extraction, and, on the basis of infra-red evidence, gives also butenolide (XIV), by isomerization to the *cis* isomer; the isomerization being catalysed by ultra-violet light.

The cyclization product, butenolide (XIV), has been formulated as the result of a *trans*-addition of the carboxyl group, in view of the generally accepted *trans*-addition of nucleophilic agents to triple bonds.[12]

Butenolide (XIV) has a chromophore similar to the one present in patulin, and accordingly shows similar ultra-violet absorption. In the infra-red spectrum there are two bands in the C=O stretching range, at 1783 (s) and at 1745 (s) cm^{-1}, like other γ-methylen-α,β-butenolides[3,4] and patulin itself.[2,13] Therefore, Grove's assumption that two different species are present in patulin is not consistent. Instead, the doublet at 1780–1740 cm^{-1} seems to be intrinsic to certain γ-ylidenbut-α,β-enolide systems.[3,*†]

Mineral acid treatment of butenolide (XIV) removes the tetrahydropyranyl group and gives the corresponding hydroxy compound (XV). The acid hydrolysis in the presence of hydroxylamine hydrochloride of either product gives *a crystalline oxime* (XVI) *identical, in all respects, with oxime from natural patulin.*[14] Infra-red spectrum, not previously reported, shows bands at 3333–2700 (s), 1745 (s), 1667 (w), 1623 (w), and at 1585 (m) cm^{-1} (in KBr).

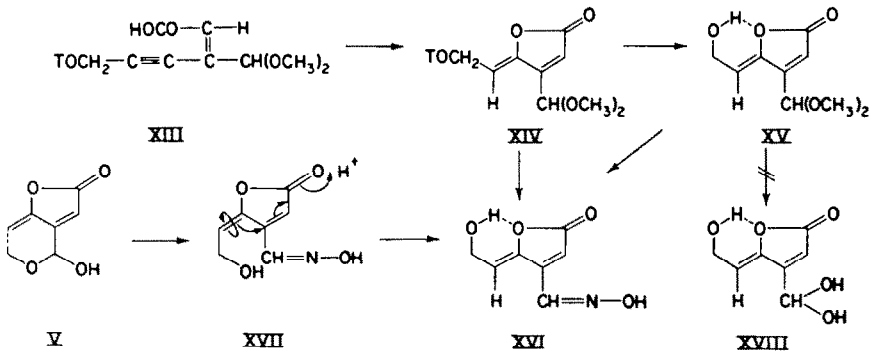
Since the synthetic product has a *trans*-configuration, the opening of the cyclic hemiacetal function in natural patulin, to give carbonyl derivatives, must proceed with isomerization. Atomic models illustrate the manner in which *cis* forms are hindered, unless cyclization takes place, as in patulin itself. The postulated acid-isomerization, similar to that of *cis*-α,β-ethylenic acetals to the free *trans*-aldehydes,[15] can be easily visualized (XVII).

The stereomutation in the formation of carbonyl derivatives from patulin, is also evidenced by the fact that the oxime is better prepared from the synthetic product XIV or XV than from patulin. From the latter, several recrystallizations are necessary to get a sharp melting point of the derivative, and observation of the crude oxime in the Kofler microscope shows clearly a mixture of crystals. Probably, the initial derivative

* Work in progress in this Laboratory.

† *Note added in proof:* Recently we have been acquainted with the paper by R. N. Jones *et al.* [*Canad. J. Chem.* **37**, 2007 (1959)] where the splitting of the C—O stretching band is established as a general feature in certain types of unsaturated lactones. The solvent effects observed are also in agreement with our observations.

[11] J. L. H. Allan, G. D. Meakins and M. C. Whiting, *J. Chem. Soc.* 1874 (1955).
[12] R. A. Raphael, *J. Chem. Soc.* 2433 (1959) and references therein.
[13] J. F. Grove, *J. Chem. Soc.* 883 (1951).
[14] F. Bergel, A. L. Morrison, A. R. Moss and H. Rinderknecht, *J. Chem. Soc.* 415 (1944).
[15] R. A. Raphael and F. Sondheimer, *J. Chem. Soc.* 2693 (1951).



from patulin has a *cis*-configuration (XVII), and slowly rearranges to the more stable *trans*-isomer. If, eventually, it crystallizes rapidly from the reaction mixture, a product with unsharp melting point, starting at 114°, and broad bands in the infra-red spectrum is obtained. Consequently, the oxime is a derivative of the hypothetic "*trans*-patulin".

Other carbonyl derivatives, such as phenylhydrazones, are conveniently prepared from the oxime, by the usual technique, and their physical constants agree with previously reported data.[14]

The attempts to hydrolyse the dimethylacetal (XIV or XV), and the subsequent isomerization to patulin, have been unsuccessful, the acetal group showing an unusual stability to acids. Stronger acid hydrolysis leads to sugar-like alteration products, rather than to the expected compounds. Sulphuric, hydrochloric, perchloric, acetic and formic acids have been tried.

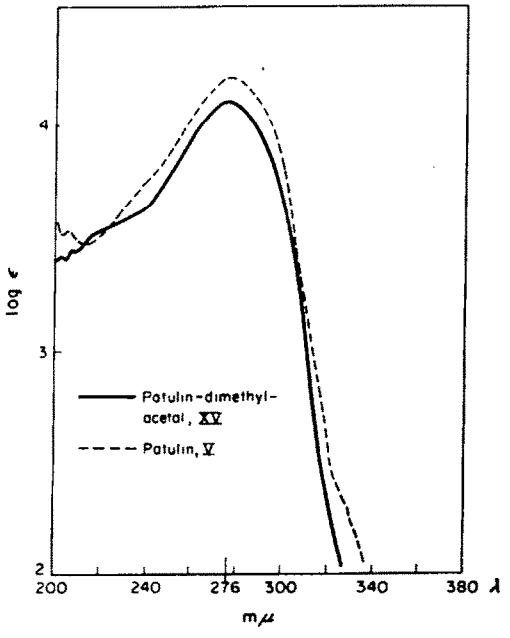


FIG. 1.

Isomerization of the dimethylacetal (XV) by ultra-violet light, whether in acid medium or not, with an eventual *intra*-transacetalization leading to patulin or its methylether[14] also failed, and again none of the desired products could be detected.

The dimethylacetal can be regarded as a glyoxylic acid vinylog, or as a substituted fumaric acid semialdehyde, and this could explain the stability of the ortho-form and its breakdown under more drastic acid conditions. Hydrolysis with formic acid probably gives, on the basis of infra-red data, the aldehyde diformate (strong extra bands at 1727 and 1180 cm^{-1}). Accordingly, the hypothetic "*trans*-patulin" should be formulated as XVIII, and this structure justifies the sugar like products formed in acid conditions, and the infra-red spectra, in the "finger-print" region, resemble those of similar polyhydroxylated compounds (i.e., ascorbic acid).

EXPERIMENTAL

Ultra-violet spectra were determined with an *Uvispek* Hilger Spectrophotometer, and the infra-red spectra recorded in an *Infracord* Perkin-Elmer Spectrophotometer equipped with rock salt optics.

N-*Dimethoxyacetyl-piperidine* X

A mixture of methyl dimethoxyacetate (68 g) and piperidine (80 ml) was set aside for 48 hr, a smooth exothermic reaction taking place. The methanol formed was distilled off (18·5 ml), through a column packed with Fenske helices, and the excess piperidine removed in vacuum. The remaining product was distilled at high vacuum, collecting a single fraction (91·5 g; 97% yield), $b.p._{0.4}$ 86–88°, $n_D^{24.5}$ 1·4708 (Found: C, 57·6; H, 9·1; N, 7·35 $C_9H_{17}NO_3$ requires: C, 57·7; H, 9·15; N, 7·5%).

5-(2′-*Tetrahydropyranyloxy*)-1,1-*dimethoxy-pent*-3-*yn*-2-*one* VI b

Under an atmosphere of purified nitrogen, a solution of tetrahydropyranyl-propargyl ether[16] (14·0 g) in benzene (200 ml) was added to a stirred solution of ethylmagnesium bromide (prepared from 2·4 g magnesium) in ether (100 ml). After stirring for a further 2 hr, N-dimethoxyacetyl-piperidine (13·5 g) in benzene (50 ml) was added dropwise. The mixture was stirred for 2 hr, heated under reflux for 2–3 hr and left overnight. The mixture was then poured into ice-cooled dil 1 N H_2SO_4 (200 ml), shaken for a few minutes and worked up as usual.

The solvents were removed in the vacuum and the 5-hydroxypentanal generated distilled off (4·0 g). The residual oil was distilled at high vacuum: deep yellow liquid, $b.p._{0.025}$ 112–115° (9·4 g; 53% yield). The infra-red spectrum showed some N-dimethoxyacetyl-piperidine present as impurity, but the product was suitable for the next operation.

The analytical sample was an almost colorless liquid, n_D^{17} 1·4772, λ_{max} 223 mμ (ε = 6·160) (cyclohexane) (Found: C, 59·3; H, 7·5 $C_{12}H_{18}O_5$ requires: C, 59·5; H, 7·5%).

Methyl 6-(2′-*tetrahydropyranyloxy*)-3-*dimethoxymethyl-hex*-4-*yn*-2-*enoate* VIII b

A solution of the acetylenic ketoacetal (VI b, 5·8 g) and carbomethoxymethylen-triphenylphosphorane[17] (8·0 g) in benzene (160 ml) was refluxed, under nitrogen, for 24 hr. The dark solution was passed through a column of neutral aluminium oxide (100 ml), and the column washed with ether (300 ml). The solvents were removed, and the semisolid residue treated with ether. Most of the triphenylphosphine oxide crystallized, and was filtered off. The filtrate was evaporated, and the remaining triphenylphosphine oxide was precipitated with petrol ether. The petrol ether extract was evaporated once again, and the oily residue distilled at high vacuum, the fraction $b.p._{0.001}$ 114–115° being collected (4·2 g; 60% yield).

The analytical sample was a pale yellow liquid, $n_D^{16.5}$ 1·5013; λ_{max} 257 mμ (ε = 11·400) (cyclohexane) (Found: C, 60·5; H, 7·6 $C_{15}H_{22}O_6$ requires: C, 60·4; H, 7·4%).

β-*Dimethoxymethyl*-γ-(2′-*tetrahydropyranyloxymethyl*)-*methylen*-α,β-*butenolide* XIV

(a) *Hydrolysis.* Ester (VIII b, 3·7 g) was treated with 0.5 N NaOH (32 ml) and the mixture

[16] H. B. Henbest, E. R. H. Jones and I. M. S. Walls, *J. Chem. Soc.* 3646 (1940).
[17] O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser and P. Zeller, *Helv. Chim. Acta* **40**, 1242 (1957).

vigorously shaken for 2 hr. The homogeneous solution, after standing at room temp for a further 4 hr, was filtered, washed with ether and, cooling with ice, was acidified with dil sulphuric acid. The cloudy emulsion was extracted with ether, and the combined ether extracts were washed with water and dried. Evaporation of the solvents at room temp gave the acid as a yellow syrup, the infra-red spectrum indicating a pure acid; λ_{max} 246 mμ (ε ~11.000).

(b) *Isomerization.* The crude acid was dissolved in methanol (17 ml) and 2 drops of aqueous silver nitrate solution (4%) were added. An exothermic reaction took place, and the mixture was left 4 hr at room temp. The methanol was removed, and the oily residue extracted with ether, filtered, and washed with sodium bicarbonate solution (Sol. A) and water. The ether solution was dried and evaporated, affording butenolide (XIV; 2·8 g; 80% yield) as a yellow oil. Distillation at high vacuum, b.p.$_{0\cdot01}$ 137–138°, gave pure butenolide (2·1 g; 60% yield).

The analytical sample was a yellow oil, n_D^{23} 1·5165; λ_{max} 281 mμ (ε = 12·400) (ethanol) (Found: C, 58·8; H, 7·4 $C_{14}H_{20}O_6$ requires: C, 59·1; H, 7·1%).

When the sodium bicarbonate solution (Sol. A) was acidified and extracted with ether, impure *trans*-acid (0·25 g; 7% yield) was obtained. Chromatography over silica gave a fairly pure *trans*-acid, with some lactonic impurity; λ_{max} 250 mμ (ethanol) (Found: C, 59·4; H, 7·6%).

β-Dimethoxymethyl-γ-hydroxymethylmethylen-α,β-butenolide (patulin-dimethylacetal) XV

Butenolide (XIV; 1·3 g) was treated with dil 1 N HCl (16 ml) the mixture was shaken for 1 hr, and then set aside for 24 hr. The yellow solution was neutralized with silver carbonate, filtered, and the water removed in vacuo. (Alternatively, the acid solution was neutralized with barium carbonate, filtered and extracted with ethyl acetate). The residue was extracted with ether, dried and evaporated, yielding the product as a yellow oil (0·70 g; 76% yield, dried at high vacuum for several hr).

A sample redistilled for analysis (bath temp 130°; press 0·001 mm) gave an almost colorless oil; λ_{max} 276 mμ (ε = 12·200) (ethanol) (Found: C, 54·5; H, 6·5 $C_9H_{12}O_5$ requires: C, 54·0; H, 6·0%).

Patulin-oxime XVI

Freshly distilled butenolide (XIV, 0·50 g) was treated with a solution of hydroxylamine hydrochloride (1·0 g) in 1 N HCl (5 ml) and the mixture shaken until a homogeneous solution was obtained. The oxime slowly crystallized during about 2–3 days and after recrystallization from water (colorless needles; 0·21 g; 73% yield) had m.p. 152·5–154° (dec) (Kofler) and mixed m.p. with an authentical sample from patulin[14] (m.p. 152–153°) 152–154°; $\lambda\lambda_{max}$ 206,285 mμ (ε = 9·000, 19·000) (ethanol) (Found: C, 50·0; H, 4·4; N, 8·3 $C_7H_7NO_4$ requires: C, 49·7; H, 4·2; N, 8·3%).

Similarly, patulin-oxime was prepared from hydroxy-butenolide (XV), with somewhat lower yields.

Acknowledgements—The author wishes to acknowledge his indebtedness to Professor J. Pascual and Professor E. R. H. Jones for their kind interest in the present work, and for helpful suggestions; and to the latter for a sample of patulin (from Roche Products Ltd.); to Dr. J. Castells for valuable comments on the infra-red spectra; to Dr. J. Estevan for the analyses; and, finally, to "Fundación Juan March" for financial support.