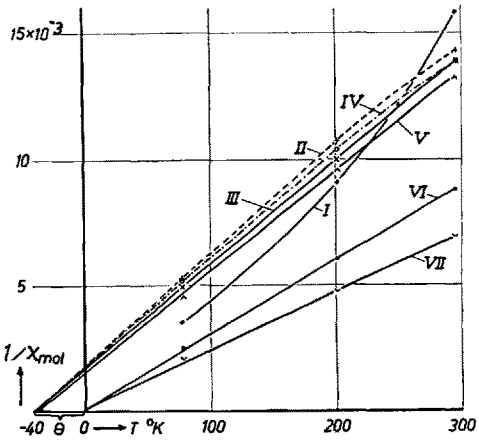
Magnetische Eigenschaften des Ferritins und einiger Eisen(III)-Komplexe von Aminosäuren bei 22°C

Nr.	Verbindung	*MG*	$\chi_{mol} \cdot 10^6$	μ_{eff}
I	Ferritin	330*	6200	3,84
II	Dihydroxo-dileucino-eisen(III)-chlorid [$R = -CH_2\text{-}CH(CH_3)_2$] . . .	388	7000	4,08
III	Dihydroxo-diisoleucino-eisen(III)-chlorid [$R = -CH(CH_3)\text{-}CH_2\text{-}CH_3$] .	388	7200	4,14
IV	Dihydroxo-divalino-eisen(III)-chlorid [$R = -CH(CH_3)_2$]	360	7200	4,14
V	Dihydroxo-dimethionino-eisen(III)-chlorid ($R = -CH_2\text{-}CH_2\text{-}S\text{-}CH_3$) . .	423	7400	4,20
VI	Dihydroxo-diphenylalanino-. eisen(III)-chlorid · HCl ($R = -CH_2\text{-}C_6H_5$)	492	11300	5,18
VII	Dihydroxo-dilysino-eisen-(III)-chlorid · 7 H_2O · 2 HCl [$R = -(CH_2)_4\text{-}NH_2$]	616	14500	5,87

* Äquivalentgewicht bezogen auf 1 Atom Eisen.

ständige Unterdrückung der Bahnmomente erklärt[1]. Ähnliche Werte fanden wir auch für die analytisch nicht völlig rein erhaltenen, in Tabelle 1 nicht aufgeführten Eisen(III)-Verbindungen des Leucylglycins ($\mu_{eff} = 3{,}95\mu_B$) und der Glutaminsäure ($\mu_{eff} = 3{,}80\mu_B$).



Temperaturabhängigkeit der molaren Suszeptibilitäten des Ferritins und einiger Eisen(III)-Komplexe von Aminosäuren. Die römischen Zahlen entsprechen den in der Tabelle aufgeführten Komplexen.

Der Eisenkomplex der basischen Aminosäure Lysin [VII] unterscheidet sich nicht nur durch einen Mehrgehalt von 2 Molekülen HCl je Eisenatom von den Komplexen der sauren und neutralen Aminosäuren, sondern auch durch ein magnetisches Moment, das mit dem für die 5 ungepaarten Elektronen von Eisen(III)-Salzen berechneten Spinmoment von $5{,}92\mu_B$ innerhalb der Messgenauigkeit übereinstimmt. Die Zwischenstellung des Komplexes der aromatischen Aminosäure Phenylalanin [VI], der 1 Molekül HCl je Eisenatom enthält, kommt auch in dem Wert von $\mu_{eff} = 5{,}18\mu_B$ zum Ausdruck.

Die Verbindungen VI und VII folgen, wie aus dem $^1/\chi_{mol}$-T-Diagramm in der Figur hervorgeht, innerhalb der Fehlergrenzen dem Curieschen Gesetz. Davon abweichend befolgen die kationischen Koordinationsverbindungen mit 3 ungepaarten Elektronen (II–V) das Curie-Weisssche Gesetz mit Δ-Werten von etwa -40. Die Temperaturabhängigkeit der reziproken Suszeptibilität des als Neutralkomplex erkannten Ferritins[1] lässt sich hingegen, wie aus Figur 1 hervorgeht, nicht durch eine Gerade darstellen. Derartige Abweichungen vom Curieschen Gesetz, die bei verschiedenen Liganden bzw. Ionen an ein und demselben Schwermetallatom in verschiedener Form auftreten, lassen sich nach VAN VLECK[2] durch Heisenbergsche Austauschkräfte sowie durch unvollständige Unterdrückung der Bahnmomente erklären.

Die für die Eisen(III)-Komplexe I–V ermittelten magnetischen Momente zeigen, dass in diesen Verbindungen 3 ungepaarte Elektronen je Eisenatom vorhanden sind, woraus nach der Paulingschen Theorie folgt, dass die 4 Liganden die Ecken eines Planquadrates besetzen. Damit ist unseres Wissens erstmals an Substanzen in fester Form gezeigt worden, dass ein und dasselbe Zentralatom magnetisch unterscheidbare Durchdringungskomplexe mit 2 verschiedenen Koordinationszahlen auszubilden vermag.

E. BAYER dankt der Deutschen Forschungsgemeinschaft für Gewährung eines Stipendiums und Herrn Dozent Dr. H.-J. BIELIG für anregende Diskussionen. Bei der Ausführung der magnetischen Messungen haben uns die Herren A. ÜBERLE und F. LEIBLE unterstützt.

E. BAYER[3] und K. H. HAUSER

Max-Planck-Institut für Medizinische Forschung, Institut für Chemie, Heidelberg, den 4. April 1955.

Summary

Magnetic measurements on iron(III)-complexes of amino acids show that in these compounds, as also in Ferritin, there are 3 unpaired electrons for each iron atom. From this it follows that, according to the Pauling theory, there is a square-planar arrangement of the 4 ligands.

[1] H.-J. BIELIG und E. BAYER, Naturwissenschaften *42*, 125 (1955); Chem. Ber., im Druck (1955).

[2] J. H. VAN VLECK, *The Theory of Electric and Magnetic Susceptibilities* (Clarendon Press, Oxford 1932), S. 304.

[3] Jetzige Adresse: Biochemische Abteilung des Forschungs-Instituts für Rebenzüchtung Geilweilerhof, Siebeldingen (Pfalz).

DISPUTANDUM

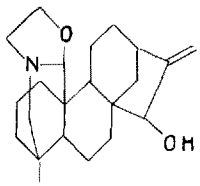
The Basicity and Steric Configuration of the Diterpene Alkaloids Veatchine and Atisine

In a recent paper[1], we suggested that veatchine and anhydrous garryine may be represented by the structures I and II respectively. While the evidence for these

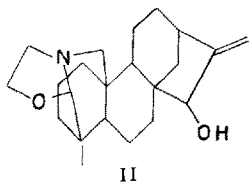
[1] L. PAULING, *Nature of the Chemical Bond* (Cornell University Press, 2. ed. 1948), S. 114.

[1] K. WIESNER, R. ARMSTRONG, M. F. BARTLETT, J. A. EDWARDS, J. A. C. S. *76*, 4858 (1954); Chem. and Ind. *1954*, 132.

structures seemed fairly conclusive, the decision as to which of the two formulae belongs to veatchine and which to garryine was based mainly on considerations involving the basicities of the two compounds (veatchine pK_a 11·5; garryine pK_a 8·7) and certain assumptions about the stereochemistry of the skeleton. We have now obtained direct evidence that the assignment of the two formulae is correct. Consequently it is now proper to discuss the reasons for the difference in the basicities of veatchine and garryine, since they have a bearing on the stereochemistry of the skeleton.

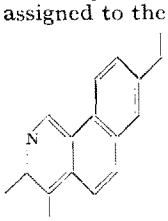


I

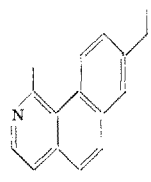


II

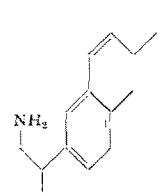
We have already reported[1] the preparation of ethyldihydrogarryine by the reaction between anhydrous garryine and ethylmagnesiumbromide and the dehydrogenation of this compound to an azaphenanthrene $C_{18}H_{19}N$. The analogous reaction of veatchine with ethylmagnesiumbromide gave a mixture of products from which a pure compound could not be isolated. We have now repeated these reactions with methylmagnesiumiodide in the hope of obtaining methyldihydroveatchine also. While methyldihydrogarryine was obtained quantitatively as a crystalline substance (m.p. 139–140°C), methyldihydroveatchine was isolated in lower yield only after counter-current distribution of the oily products and crystallization of the picrate (m.p. 216–218°C). Dehydrogenation of methyldihydrogarryine gave an azaphenanthrene $C_{17}H_{17}N$ (m.p. 129°C). The U.V. spectrum of this compound is identical with that of the previously reported azaphenanthrene $C_{18}H_{19}N$ from ethyldihydrogarryine. There are two possible structures (III and IV) for the methyldihydrogarryine dehydrogenation product. It is clear that if garryine is represented by II, the azaphenanthrene derived from methyldihydrogarryine will be III. We have synthesized compound IV by subjecting the N-acetyl derivative of the previously described[2] compound V to a cyclisation with phosphorus oxychloride, followed by dehydrogenation. The synthetic compound (m.p. 44–45°C) was not identical with the dehydrogenation product of methyldihydrogarryine, which leaves the structure III to be assigned to the latter.



III



IV



V

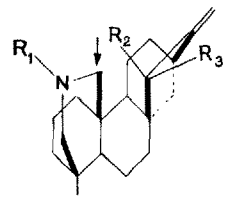
[1] K. Wiesner, W. I. Taylor, S. K. Figdor, M. F. Bartlett, J. R. Armstrong, and J. A. Edwards, Chem. Ber. deutsch. Ges. *86*, 800 (1953).

[2] M. F. Bartlett and K. Wiesner, Chem. and Ind. *1954*, 542.

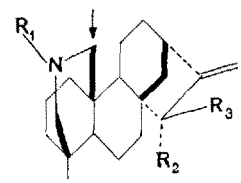
The possibility[1] that both garryine and veatchine are represented by the structure II and that the difference between them is due only to the configuration of the carbon carrying the ether oxygen can be invalidated on other grounds[2].

We have also attempted to corroborate these conclusions by subjecting methyldihydroveatchine to a selenium dehydrogenation. However, with the amount of methyldihydroveatchine available only traces of base were obtained. It will become clear from the following discussion that in methyldihydroveatchine the nitrogen ring is strained because of the crowded condition of the methyl-group. Consequently in the dehydrogenation process the nitrogen ring breaks preferentially and only 1-methyl-7-ethyl phenanthrene can be isolated in good yield. We may therefore consider the assignment of structures I and II to veatchine and garryine as established experimentally and turn to the consideration of the different basicities of the two compounds.

There are two possibilities VI and VII for the steric structure of the garrya alkaloids which deserve serious consideration.



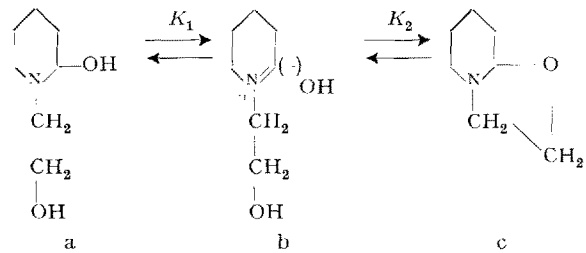
VI



VII

Both of these structures have in common that the position marked by an arrow is subjected to strong steric hindrance. In all other steric arrangements there is no appreciable difference in the degree of steric hindrance of the two carbons flanking the nitrogen. It will be shown that the differences in behaviour between garryine and veatchine may be explained in terms of this steric hindrance.

We have first favoured the steric arrangement VI[3] on the grounds that in it this steric hindrance is especially large. However it is not possible to assess this aspect quantitatively and the decision between VI and VII has to be made in a different way which is discussed later.



a b c

[1] We thank Professor Carl Djerassi for bringing up this possibility in a discussion at the Sixth Summer Seminar, University of New Brunswick, August 1954.

[2] Both garryine and veatchine give salts which still retain their different identities as characterized most conveniently by potentiometric titration. The pK value found by titration of garryine and veatchine hydrochlorides are identical with those found by the titration of the free bases. Again, basification of a solution of veatchine and garryine hydrochlorides leads to isolation of pure veatchine and garryine respectively, and not to the isolation of an equilibrium mixture of the same composition in both cases, as might be expected if the above assumption was correct.

[3] K. Wiesner, R. Armstrong, M. F. Bartlett, J. A. Edwards, J. A. C. S. *76*, 4858 (1954); Chem. and Ind. *1954*, 132.

A solution of veatchine or garryine in aqueous media contains an equilibrium mixture of the species *a*, *b* and *c*, represented by partial structures.

Many experiments devised to trap or detect an open chain aldehyde tautomer failed and consequently this species may be neglected in the equilibrium. It is clear that the basicity of garryine and veatchine is a function of the equilibrium constants K_1 and K_2.

$$K_1 = \frac{[b]\cdot[^-OH]}{[a]} \qquad K_2 = \frac{[b]\cdot[^-OH]}{[c]} \tag{1}$$

The equilibrium between the quaternary hydroxide *b* and the other species is given by equation 2.

$$\frac{[b]\cdot[^-OH]}{[a]+[c]} = \frac{K_1\cdot K_2}{K_1+K_2} . \tag{2}$$

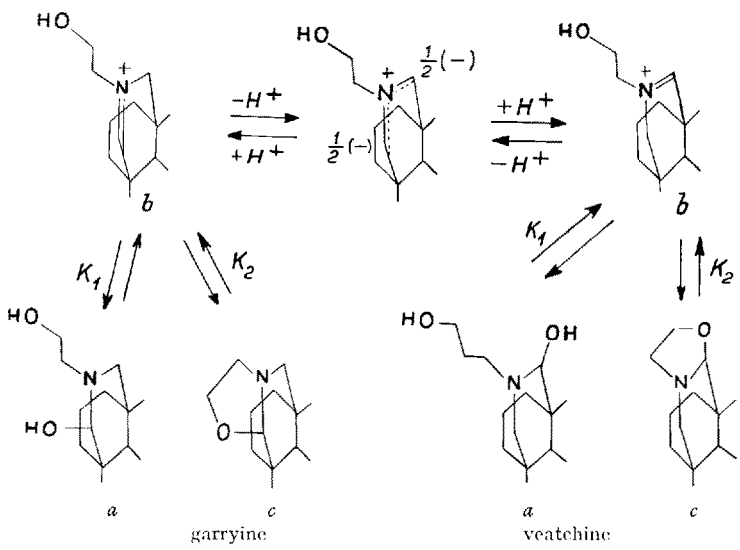
Since $[H^+]\cdot[^-OH] = Kw$ we can transform equation 2 into 3.

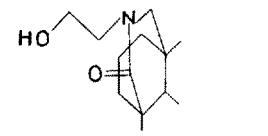
$$\frac{([a]+[c])\cdot[H^+]}{[b]} = \frac{K_1+K_2}{K_1\cdot K_2}\,Kw = K_A . \tag{3}$$

In equation 3, K_A is the titrated acidity of the conjugate acid *b*. Further equation 4 is easily derived and gives the ratio of the carbinolamine and ether forms.

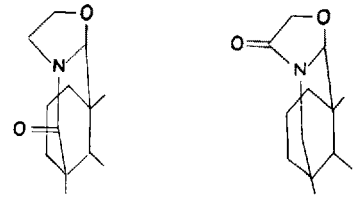
$$\frac{[a]}{[c]} = \frac{K_2}{K_1} . \tag{4}$$

The mechanism of conversion of the quaternary Schiff base *b* into the ether *c* or carbinolamine *a* is obviously an attack of an electron pair of either the oxygen of the primary hydroxyl group or of a hydroxyl ion on the carbon of the $-C=\overset{|}{\underset{+}{N}}-$ group in *b*. From models of garryine and veatchine built on the basis of the stereochemistry given in formulas VI and VII, it is clear that while such an attack is unhindered in garryine, it is subjected to strong steric hindrance in veatchine. This steric hindrance is especially pronounced in the formation of carbinolamine, and smaller in the formation of ether. The carbinolamine form of veatchine is strained and difficult to construct from scale models. If these ideas are now expressed in terms of the two equilibrium constants K_1 and K_2, it appears that K_1 of veatchine must be much larger than the same constant of garryine, whereas K_2 in veatchine may be only moderately larger than the K_2 of garryine. Equation 3 then shows clearly that veatchine is a stronger base than garryine. Equation 4 gives the ratio between the carbinolamine and ether forms and shows clearly that in veatchine this ratio is shifted in favour of the ether form with respect to garryine. This is in agreement with the various reactions of the two compounds described in our previous communications[1].





VIII



IX X

Finally it should be pointed out that the different reactivities of garryine and veatchine with methylmagnesiumiodide are caused by the same factors which lead to the difference in the ease of attack on the quaternary forms of garryine and veatchine by a hydroxyl ion.

Another interesting reaction is the conversion of veatchine to garryine by hot alkali. In this medium the quaternary forms of garryine and veatchine are undoubtedly in equilibrium with an ylid ion.

Because of the large concentration of alkali the bulk of the substance will be present in the equilibrium as forms *a* and *c* and only a negligible amount will be present as the quaternary bases *b*. It is therefore obvious that the equilibrium must be shifted toward the sterically favourable forms of garryine and not the strained forms *a* and *c* of veatchine. *Thus it is seen that the manifold behaviour of garryine and veatchine may be reduced to a common denominator and is governed by the large steric hindrance of the carbinolamine and similar derivatives of veatchine as compared to garryine.*

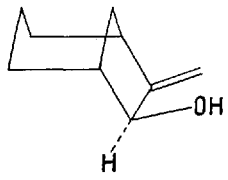
In order to differentiate between the steric structures VI and VII the two epimeric alcohols represented by VI or VII

[$R_1 = C_2H_5$, $R_2 = H$, $R_3 = OH$ and $R_1 = C_2H_5$, $R_2 = OH$, $R_3 = H$]

and their acetates were prepared. It is easily seen from models that if structure VI was correct there would be considerably more interaction between a hydroxy or acetoxy group and the nitrogen in one of the two epimers than in the other. On the other hand in the structure VII such an interaction would be negligible in both epimers. The basicities of all four compounds were determined and found to be approximately the same ($pK \sim 7{\cdot}4$). This

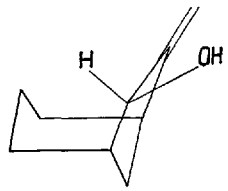
[1] In this connection, the different courses of the permanganate oxidation of veatchine and garryine are especially characteristic. Garryine is oxidised to oxogarryine VIII, while veatchine gives under the same conditions equal amounts of two oxoveatchines IX and X.

finding leaves us with VII as the more probable steric arrangement. The problem remains now to assign the configuration to the hydroxy group of garryine and veatchine and also to the methyl group in the tetrahydroproducts. The available evidence concerning this matter permits to assign to the hydroxy group of veatchine the configuration given in the partial structure XI*a*.



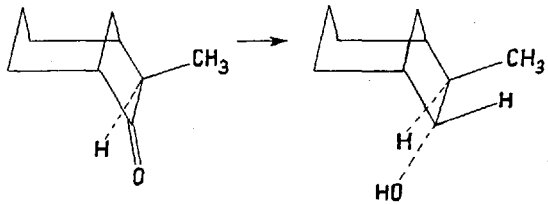
XI*a*

At this point we must emphasize that the subsequent considerations are unchanged whether we adopt the stereochemistry VI or VII and consequently only the evidence already cited may serve to choose between the two. Partial formula XI*b* would depict veatchine if VI was correct.



XI*b*

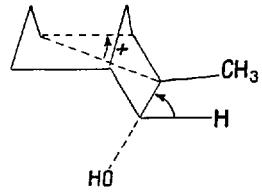
Ketonic derivatives of veatchine obtained either by oxidation of the secondary hydroxy group or by pyrolytic isomerisation of the allylic alcohol into a ketone are reduced by $LiAlH_4$ to form alcohols with the hydroxy group in the epi-configuration. This can be assumed to take place by approach of the reagent from the less hindered side.



XII XIII

These considerations are borne out by the finding that acetyl derivatives of compounds with the hydroxyl-group in the veatchine configuration (quasi-equatorial) are formed and saponified with greater ease than the corresponding epimers (quasi-axial). The configuration of the methyl-group in various derivatives is the same whether these have been obtained by hydrogenation of the exocyclic double bond or isomerisation of an allylic alcohol[1].

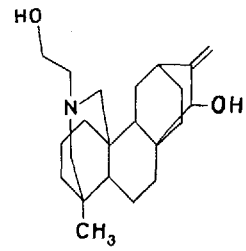
Since compounds possessing the partial structure XII are stable to alkali, they must possess the configuration indicated in this partial structure with the methyl group in the quasi-equatorial position. Finally we should like to mention a reaction which was discovered by DJERASSI and kindly communicated to us. The named author has isolated a compound which he has shown to differ from veatchine only by the configuration of the secondary hydroxy-group. This epi-veatchine (Laurifoline) isomerizes exceedingly easily with acid into the corresponding ketone (Quachichicine) under conditions where veatchine is stable. It is clear that if our stereochemical assignment is correct it must provide a plausible explanation for this difference. The following explanation has been suggested by WOODWARD[1]. In the isomerisation of epi-veatchine the cation XIV is an intermediate.



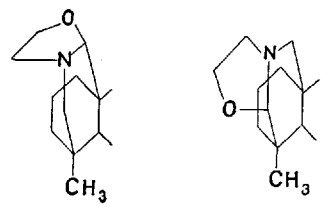
XIV

In this cation the steric arrangement is favourable for elimination of the hydrogen in the manner indicated. Such an opportunity does not exist in the corresponding epimeric cation derived from veatchine. This explanation consequently provides further support of the steric structure assigned to veatchine.

We have some time ago assigned[2] structure XV to dihydroatisine on the basis of the similarity of most of its chemistry[3] to the chemistry of the garrya alkaloids. This implies the arbitrary assignment[4] of partial structures XVI and XVII to atisine and isoatisine.



XV



XVI XVII

Subsequently, PELLETIER and JACOBS[5] have produced additional evidence in support of these structures. As it is obvious that isoatisine in all its reactions and basicity is analogous to garryine, and atisine to veatchine, we may now assign the structure XVI to atisine and XVII to isoatisine with more confidence.

The isomerisation of atisine into isoatisine by alkali parallels therefore completely the corresponding change of veatchine into garryine the driving force of which has

[1] This follows clearly from the interrelations given in our last paper (K. WIESNER, R. ARMSTRONG, M. F. BARTLETT, J. A. EDWARDS, J. A. C. S. *76*, 4858 (1954); Chem. and Ind. *1954*, 132).

[1] R. B. WOODWARD, private communication.

[2] K. WIESNER, R. ARMSTRONG, M. F. BARTLETT, and J. A. EDWARDS, Chem. and Ind. *1954*, 132 (1954).

[3] For a summarising reference see E. S. STERN in R. H. F. MANSKE and H. L. HOLMES, *The Alkaloids*, Vol. 4 (Academic Press Inc., New York, 1955).

[4] See also M. F. BARTLETT, Ph. D. Thesis, University of New Brunswick, May 1954.

[5] S. W. PELLETIER and W. A. JACOBS, J. Amer. Chem. Sci. *76*, 4496 (1954).

been already discussed. EDWARDS and SINGH[1] have just described a conversion of isoatisine hydrochloride with acetic anhydride into a "triacetate hydrochloride" which on mild hydrolysis with sodium carbonate gives atisine. The change of an iso-atisine derivative which is completely fixed in the quarternary form (*b*) into an atisine derivative (also fixed in this form) is to be expected as in this case the stabilities will be reversed, the derivative with the trigonal carbon in the more hindered position being more stable. However the triacetate hydrochloride obviously must have been a diacetate hydrochloride with a mole of acetic acid.

Acknowledgements. We wish to thank the John Simon Guggenheim Foundation (K. W.) and the National Research Council of Canada (J.A.E.) for the award of fellowships, as well as the University of New Brunswick for a leave of absence to one of us (K.W.). We further express our appreciation to Professor CARL DJERASSI for communicating his work to us prior to publication. Finally it is a pleasant duty to thank Professor R. B. WOODWARD for the hospitality extended to one uf us in his laboratory and for a discussion concerning the isomerisation of veatchine and its epimer by acid.

K. WIESNER and J. A. EDWARDS

Converse Memorial Laboratories, Harvard University, Cambridge, Mass. USA, and University of Brunswick, Fredericton, New Brunswick, Canada, February 2, 1955.

Zusammenfassung

Die Basizität und das verschiedene chemische Verhalten der Isomerenpaare Veatchin-Garryin und Atisin-Isoatisin werden mit der sterischen Konfiguration dieser Verbindungen in Zusammenhang gebracht.

[1] O. E. EDWARDS and TARA SINGH, Can. J. Chem. *33*, 448 (1955).

Über einen möglichen Weg der Biosynthese der Carotinoide bei *Mucor hiemalis*

In einer früheren Arbeit über die Biogenese der Carotinoide bei *Phycomyces blakesleanus*[1] hatten wir berichtet, dass eine Reihe organischer Säuren in der Lage sind, die Carotinbildung auf einem nichtcarotinogenen Nährmilieu[1] auszulösen. Als aktive Vertreter der Fettsäuren fanden wir die Essigsäure, die Buttersäure und die Palmitinsäure. Unter den Ketosäuren erwies sich als besonders aktiv die Brenztraubensäure, was auch durch ARNAKI und STARY[2] bei der *Sarcina lutea* bestätigt werden konnte. Unter den Dicarbonsäuren sind Oxalsäure, Malonsäure und Adipinsäure geprüft worden, die alle ausserstande sind, Carotinoide zu bilden. Hingegen ermöglichen die Weinsäure (Oxydicarbonsäure) und Zitronensäure (Oxytricarbonsäure) die Produktion reichlicher Carotinoidmengen.

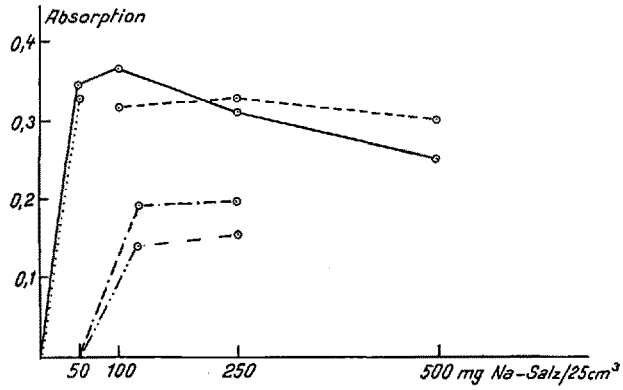


Abb. 1. Die Bildung von Carotinoiden durch verschiedene organische Säuren bei *Phycomyces blakesleanus*.
– – – – – – – Essigsäure, ····· Buttersäure;
——— Brenztraubensäure; –·–·–·– Weinsäure;
–··–··–·· Zitronensäure.
gemessen im Hilger Colorimeter. Filter Ilford 601.

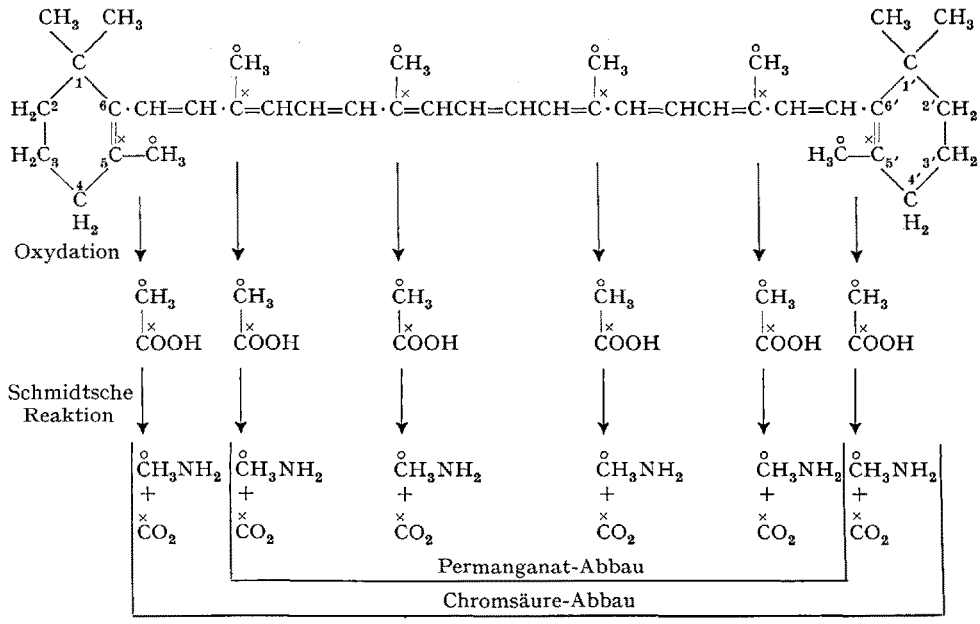
PAECH[3] machte es uns zum Vorwurf, die Essigsäure als einzige mögliche Vorstufe der Carotinoide in Betracht zu ziehen, was, wie aus dem oben Gesagten hervorgeht, keineswegs zutrifft.

[1] W. H. SCHOPFER und E. C. GROB, Exper. *6*, 419 (1950).

[1] Wir berichtigen hier, dass auf dem nichtcarotinogenen Laktatmilieu doch sehr kleine Mengen Carotinoide gebildet werden.

[2] M. ARNAKI und Z. STARY, Biochem. Z. *323*, 367 (1952).

[3] K. PAECH, VIII[e] Congr. int. Bot. Rapports et communications Sect. 11/12, p. 49 (1954).



° stammt aus der CH_3-Gruppe der Essigsäure
× stammt aus der COOH-Gruppe der Essigsäure.