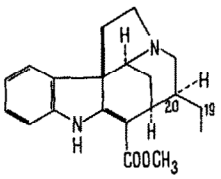
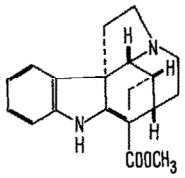
Ableitung der absoluten Konfiguration von Alkaloiden der Aspidospermingruppe durch optischen Vergleich mit Alkaloiden der Strychningruppe

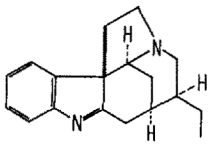
In einer kürzlich veröffentlichten Mitteilung[1] wurde durch chemische Korrelation mit den in ihrer absoluten Konfiguration bekannten stark linksdrehenden Alkaloiden 19,20-Dihydroakuammicin (I) und Tubifolin (II) gezeigt, dass den stark rechtsdrehenden Basen Tubotaiwin (= 19,20-Dihydrocondylocarpin) (III) und Condylofolin (IV) die nachstehende absolute Konfiguration zukommt.



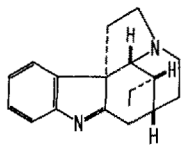
19,20-Dihydroakuammicin (I)
$[M]_D^{CH_3OH} - 2065°$



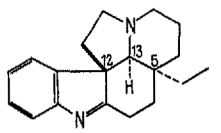
Tubotaiwin (III)
$[M]_D^{CHCl_3} + 1936°$



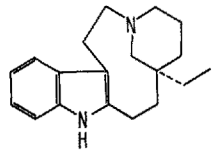
Tubifolin (II); $[M]_D^{C_2H_5OH} - 831°$,
in $CHCl_3$ $-911°$, in Essigester $-962°$



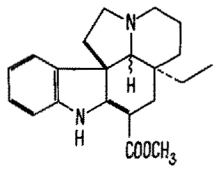
Condyfolin (IV)
$[M]_D^{Essigester} + 927°$



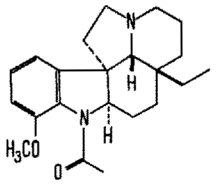
(−)-1,2-Dehydroaspidospermidin (V): $[M]_D^{C_2H_5OH} - 681°$



(+)-Quebrachamin (VI)



(−)-Vincadifformin (VIII)
$[M]_D^{C_2H_5OH} - 1821°$



(−)-Aspidospermin (VII)

Strukturell und damit in ihrem molekularen Bau sehr nahe verwandt mit Tubifolin und Condyfolin sind das stark rechts- bzw. linksdrehende (+)[2]- und (−)[3]-1,2-Dehydroaspidospermidin (V)[4].

(−)-V zeigt eine ähnliche Molekularrotation wie Tubifolin und der (bisher in der Natur noch nicht angetroffene) Antipode von Condyfolin. Diese drei Stoffe besitzen dasselbe chromophore Zentrum. Wo dieses Zentrum auch immer ist, es lassen sich daran räumliche Oktanden anlegen, die in allen drei Verbindungen die gleichen zum Zentrum nächstgelegenen Substituenten in den gleichen Oktanden enthalten. Dem (−)-1,2-Dehydroaspidospermidin lässt sich daher die absolute Konfiguration V (dem rechtsdrehenden die spiegelbildliche) zuschreiben.

Die Bildung von (+)-Quebrachamin[2,3] aus (−)-V zeigt, dass dem ersteren die absolute Stereochemie VI zukommt. (−)-Aspidospermin besitzt am C-5 die gleiche absolute Konfiguration wie (−)-Quebrachamin[5], so dass ihm die absolute Konfiguration VII zugeschrieben werden kann.

(−)-Vincadifformin[3] ($[M]_D = -1821°$) geht durch Decarbomethoxylierung in (−)-V über und besitzt daher die absolute Konfiguration VIII[6].

Zur Zeit wird versucht, durch RD-Messungen unter Heranziehung weiterer Relais-Substanzen den vorgeschlagenen konfigurativen Zusammenhang zwischen Strychnin- und Aspidosperminalkaloiden zu erhärten[7].

Summary. The absolute configuration of certain alkaloids of the Aspidospermin group is suggested.

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Organish-Chemisches Institut der Universität, Zürich (Schweiz), 21. Dezember 1963.

[1] D. SCHUMANN und H. SCHMID, Helv. chim. Acta *46*, 1996 (1963).
[2] G. F. SMITH und M. A. WAHID, J. chem. Soc. *1963*, 4002. Das (+)-1,2-Dehydroaspidospermidin zeigt $[\alpha]_D^{C_2H_5OH} = +243°$.
[3] M. PLAT, J. LE MEN, M.-M. JANOT, J. M. WILSON, H. BUDZIKIEWICZ, L. J. DURHAM, Y. NAKAGAWA und C. DJERASSI, Tetrahedron Letters No. 7, 271 (1962). (−)-1,2-Dehydroaspidospermidin zeigt $[\alpha]_D^{C_2H_5OH} = -225°$.
[4] Für die relative, der stabilsten Anordnung entsprechende Konfiguration dieses Alkaloids existieren gute Argumente: [2], sowie G. STORK und J. E. DOLFINI, J. Amer. chem. Soc. *85*, 2872 (1963) (Fussnote 9).
[5] K. BIEMANN und G. SPITELLER, J. Amer. chem. Soc. *84*, 4578 (1962).
[6] Die französischen und amerikanischen Autoren haben auf Grund von NMR-Argumenten für das Alkaloid das gespannte System mit *cis*-Stellung des H-Atoms am C-13 und der Äthylenbrücke am C-12 vorgeschlagen, was die Molekülgestalt gegenüber einer *trans*-Anordnung deutlich verändert; vgl. hierzu[3].
[7] Dem Schweizerischen Nationalfonds danken wir für Unterstützung.

5-Azacytidine, a New, Highly Effective Cancerostatic

In the course of studies on the azapyrimidines as potential inhibitors of nucleic acid biosynthesis, a method for the synthesis of nucleosides derived from 5-azacytosine has recently been developed in the laboratories[1].

Biological testing of these compounds has revealed that the cytidine analogue, 5-azacytidine (5-AzCR, m.p. 230°), The substance, in very small concentrations, inhibits the growth of some bacteria. Thus the growth of *E. coli* B in a synthetic medium is inhibited to the extent of 50% at concentrations of 0.25 μg 5-AzCR per ml, in strong contrast to a weak bacteriostatic effect (50% growth inhibition at 520 μg per ml) shown by the 6-azacytidine which also

[1] F. ŠORM and A. PÍSKALA, Coll. Czech. chem. Commun., in press. –

Table I. Effect of 5-azacytidine on lymphoid leukaemia in AK inbred mice

Dose of 5-azacytidine and no. of doses i.p.	No. of leukaemic deaths after 20 days	% 20-day survivors
100 mg/kg 1 ×	1[a]/8	75[b]
10 mg/kg 5 ×, alternate day schedule	0/8	100
5 mg/kg 7 ×, daily	1[a]/8	87.5

Eight control mice died after 6.6 ± 0.5 days of leukaemia. Therapy initiated always 24 h after inoculation of leukaemic cells (10^7). – [a] 18th day after inoculation. [b] 1 mouse died on the tenth day of intestinal haemorrhage, lymphoid hypoplasia and bone-marrow depression without macroscopical or cytological signs of leukaemia.

Table II. Effect of various cancerostatic substances on lymphoid leukaemia in AK inbred mice

Substance tested	Dose and no. of doses i.p.	% response[a]
4-Amino-pteroyl-glutamic acid	0.250 mg/kg 4 ×, alternate day schedule	30.5
5-Bis-(2-chloroethyl)-aminomethyluracil	0.250 mg/kg 9 ×, daily	16
6-Azauridine	500 mg/kg 6 ×, daily	36.6
6-Mercaptopurine riboside	10 mg/kg 7 ×, daily	11

[a] Response is given in % increase in survival time. Therapy initiated always 24 h after inoculation of leukaemic cells (10^7).

possesses cancerostatic activity. Another cancerostatic of the same type, 6-azauridine, inhibits the growth of *E. coli* B by 50% at 1300 μg per ml. The inhibitory effects of 5-AzCR on *E. coli* can be reversed by uracil, uridine and cytidine; this clearly indicates that 5-AzCR is interfering with the biosynthesis of the pyrimidine components of the nucleic acids or with their incorporation into biopolymers.

5-AzCR is somewhat toxic to mammals. In mice of inbred strain AK, the acute toxicity (LD_{50}) is about 150 mg/kg. Depression of the bone marrow and the hypoplastic involution of the lymphatic system are the main toxic manifestations.

In agreement with these effects, the new antimetabolite is a potent inhibitor of the lymphoid leukaemia of the inbred AK mice (Table I). It is remarkable that even a single dose (100 mg/kg), though provoking some toxic effects, increases the survival time very considerably. The leukaemia of AK mice is relatively resistant to chemotherapy, especially as compared with lymphoid leukaemia L1210. For comparison, the effects of various well-known cancerostatic agents on AK leukaemia, as determined in our laboratory, are listed in Table II.

An extensive investigation of the new cancerostatic substance, including clinical trials, is under way.

Zusammenfassung. Die hohe bakteriostatische und cancerostatische Wirkung eines neuen Antimetaboliten, 5-Azacytidin, wird beschrieben.

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A. Čihák, and J. Veselý

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Science, Prague (Czechoslovakia), January 3, 1964.

Reaction of Gold with Collagen *in vivo*

Gold in the form of thio-complexes is successfully used in the treatment of rheumatoid arthritis, one of the so-called collagen diseases. Although this method of treatment is comparatively old, the mode of action of gold complexes has not been definitely elucidated. As it can be assumed that reaction of gold compounds with collagen is similar to that of other heavy metals, we have tried to prove experimentally the binding of gold into the collagen structure.

For this purpose collagen fibres from tail tendon of rats (RTT) of Wistar strain (*Rattus norvegicus* var. *alba*), treated with gold sodium thiosulfate ('Sanocrysin' – Dansk Chemoterapeutisk Selskab, Denmark), 2 mg/100 g of body weight per week, were subjected to electron microscope observations and to measurements of temperature of shrinkage[1], swelling[2], and contraction-relaxation[3].

We have found that, in the electromicrograph of RTT collagen from a rat treated for 18 weeks with Sanocrysin, comparatively dark. These two bands, 60 and 100 Å units wide, are 60 Å units apart. The third band in the middle of the light band is 30 Å units wide (Figure 1). As far as we are informed from the literature, this is the first case of electron microscope demonstration of the binding of gold with collagen under conditions *in vivo*.

Other methods used in our experiments were to prove the binding of gold with collagen in the earlier stages of the treatment. With the use of all methods mentioned above, distinct changes in the measured quantities were observed even after first injections of gold (Figures 2–4). From the results obtained, it can be assumed that interaction of collagen with gold is principally similar to

[1] G. C. Nutting and R. Borasky, J. Amer. Leather chem. Assoc. *43*, 96 (1948).
[2] J. Pouchlý and I. Vavruch, *Physical Chemistry of Colloid Systems* (SNTL, Prague 1960, in Czech.).
[3] Z. Deyl and J. Rosmus, Report at the I. Conference on Collagen